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Formulation development and evaluation of taste-masked atomoxetine hydrochloride orally disintegrating tablets (ODTs)

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ABSTRACT: Atomoxetine hydrochloride is a selective norepinephrine reuptake inhibitor used for the treatment of attention deficit/hyperactivity disorder. Atomoxetine hydrochloride is available in the form of capsules and oral solutions, yet it has no orally disintegrating form due to its bitter taste. ODTs are formulated to disintegrate rapidly upon contact with saliva and enable oral administration without water or chewing and offer improved patient compliance and ease of administration. Appropriate taste masking has great importance for ODTs. In this study, developing a taste-masked ODT formulation containing atomoxetine hydrochloride produced using the wet granulation method was aimed. Formulations were designed by changing the granulation agent (Hydroxypropylmethylcellulose (HPMC), Gellan gum, Veegum, Polyethylene glycol (PEG) 20000P) and active substance to granulation agent ratio (1:2, 1:3, 1:4). Each formulation was tested physically and chemically. According to the results, it was concluded that Gellan gum is more appropriate for use in ODTs for taste masking.

KEYWORDS: Atomoxetine hydrochloride; attention deficit hyperactivity disorder; orally disintegrating tablets; taste masking; wet granulation.

1. INTRODUCTION

Oral drug administration is still the most preferred route of administration for many reasons, including accurate dosing, low-cost production, non-invasiveness, ease of patient compliance with drug administration [1]. Tablets and hard gelatin capsules constitute most of the oral drug delivery systems [2]. Patients with psychological and mental disorders, including children and elderly people, bedridden patients, and patients traveling on a continuous basis with limited access to water have limited use of conventional drugs such as tablets and capsules. Therefore, the development of alternative dosage forms that will enable patients to take their medications, comply with treatment and increase their quality of life, is being worked on. These alternative dosage forms are tablets/mini tablets/microparticular systems/films and chewable tablets. Most of the studies have been focused on "Orally Disintegrating Tablets (ODTs)" [3, 4, 5].

Disintegrating tablets, according to the Drug Assessment and Research Center (CDER), are defined as; “Solid dosage forms containing the active ingredient which can be dispersed in seconds, usually quickly, when placed on the tongue”. According to the European Pharmacopoeia (Ph. Eur), they are defined as "Tablets rapidly dispersed in three minutes before ingestion". US Pharmacopoeia considers *in vitro* disintegration time for orally disintegrating tablets to be approximately 30 seconds or less [6, 7, 8].

There is no need for water or chewing during the use of ODTs. Rapid disintegration accelerates the dissolution and subsequent absorption of the drug so that the effect begins quickly. With the decrease in the dose used, the drug-specific side effects can be reduced with ODTs. ODTs can also be developed for sustained release and controlled release applications. By using conventional processes and packaging equipment, ODTs can be produced with minimum costs. For pharmaceutical companies, there are advantages such as creating business opportunities with different product forms, patent-duration extension and innovation in product life cycle management [9, 10]. On the other hand, ODTs are sensitive to temperature and humidity, often lacking mechanical strength, so they require special packaging and careful handling [6, 10, 11].

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The performance of orally disintegrating tablets is related to the technology used in their production. The ability of the tablet to be distributed in the mouth depends on the ability of the water to quickly enter the porous structure into the tablet matrix and provide rapid disintegration [6]. There are various patented and non-patented technologies for ODT production. Some of these technologies include Zydis technology, Multiflash technology, Ziplet technology, cotton candy process, and the spray drying method [6, 10, 12].

It is especially important in paediatric and geriatric patients to ensure that bitter-tasting drugs can be administered with a tolerable taste. Because of taste problems, these patients refuse to take their medication, so the effectiveness of the treatment is reduced [13, 14]. Taste masking is defined as the reduction of oral solubility of the drug by using a suitable agent or by inhibiting the interaction of the drug particles with taste buds [15, 16]. By using appropriate agents and techniques, the taste of bitter-tasting drug substances can be masked. Today, some of the techniques used in taste-masking include coating the drug with polymer and microencapsulation, masking the taste with a gelation method, and by forming salt and its derivatives [16, 17, 18]. Taste masking can be assessed using *in vitro* or *in vivo* methods. *In vivo* approaches include human taste panel studies, electrophysiological methods, and animal studies. However, a variety of innovative *in vitro* drug release studies evaluating drug release with modified pharmacopoeia methods using taste sensors (e.g. electronic tongues, E-tongue) with a specially designed apparatus, can also be used to evaluate the taste of drugs or products [19].

Atomoxetine HCl is the first non-stimulant drug approved by the US Food and Drug Administration (FDA) in 2002 for the treatment of Attention Deficit/Hyperactivity Disorder (ADHD). It is also indicated for ADHD treatment in adults, adolescents and children aged 6 years and older [20, 21]. Atomoxetine HCl has no potential for abuse and its use is not subject to control [22]. Atomoxetine formulations on the market are in the form of capsules and oral solutions. In addition to these dosage forms, a high dosage form for the patient is required. The fact that atomoxetine HCl has a bitter taste is the most important point in the formulation development studies [23, 24]. The ability to mask this taste in the formulations to be developed significantly affects the patient's compliance with the drug and the effectiveness of the treatment. In this study, it is aimed to mask the taste of atomoxetine HCl, which has a bitter taste using the wet granulation technique with different polymeric excipients and to develop it in the form of orally disintegrating tablets, unlike present dosage forms.

2. RESULTS AND DISCUSSION

There were no significant differences between the excipients and ATX to be used in the formulation compatibility studies performed by DSC during preformulation studies (Figures 1 and 2).

The details of the formulation design of the experiments are presented in Table 1. The results of the powder mixture analysis of formulations F01-F13 were examined in Table 2; the angle of response values ranged from 20 to 34, and Carr index values ranged from 11 to 25. The Hausner ratio was found to be 1.25 and below in all formulations. Results showed moderate to good flow in all of the powder mixtures in the experiments. Each of the powder mixtures was a homogenous white to off-white powder and the loss of drying values varied between 1.60% and 5.56%. Atomoxetine HCl is not sensitive to humidity. When the physical and chemical analysis results of formulations F01-F13 were discussed in Table 3, the average weight and weight uniformity results were found to meet European Pharmacopoeia specifications. In order to ensure the rapid disintegration of orally disintegrating tablets, the compression force (7.0 to 12.0 kN) was adjusted to hardness values between 2 and 4 kp (19.6 to 39.2 N). The hardness of the formulations remained constant within the above-mentioned range by adjusting the compression force in order to compare the disintegration time of the formulations prepared in different compositions [25].

The friability values of the orally disintegrating tablets varied from 0.12 to 1.12% when the hardness value was between 2 and 4 kp (19.6 to 39.2 N). In particular, when the results of formulations F04, F05 and F06 using Gellan gum as a binder-taste masking agent were examined, the increase in Gellan gum concentration was found to increase the friability value of the tablets. In the F11, F12 and F13 trials in which PEG20000P was used as a binder-taste masking agent, friability decreased as concentrations of PEG20000P increased. In contrast, when formulations F07, F08 and F09 were evaluated, the increase in Veegum concentrations and the friability value showed little variation. It is desirable for the wetting time in orally disintegrating tablets to be as minimal as possible and the percentage of water absorption to be high. Wetting time is closely related to the inner structure of tablets and to the hydrophilicity of the excipients. It is well-known that pore size in ODTs becomes smaller and wetting time increases with an increase in compression force or a decrease in porosity. A linear relationship is present between wetting time and disintegration time. Thus, wetting time is important in the disintegration process [25].

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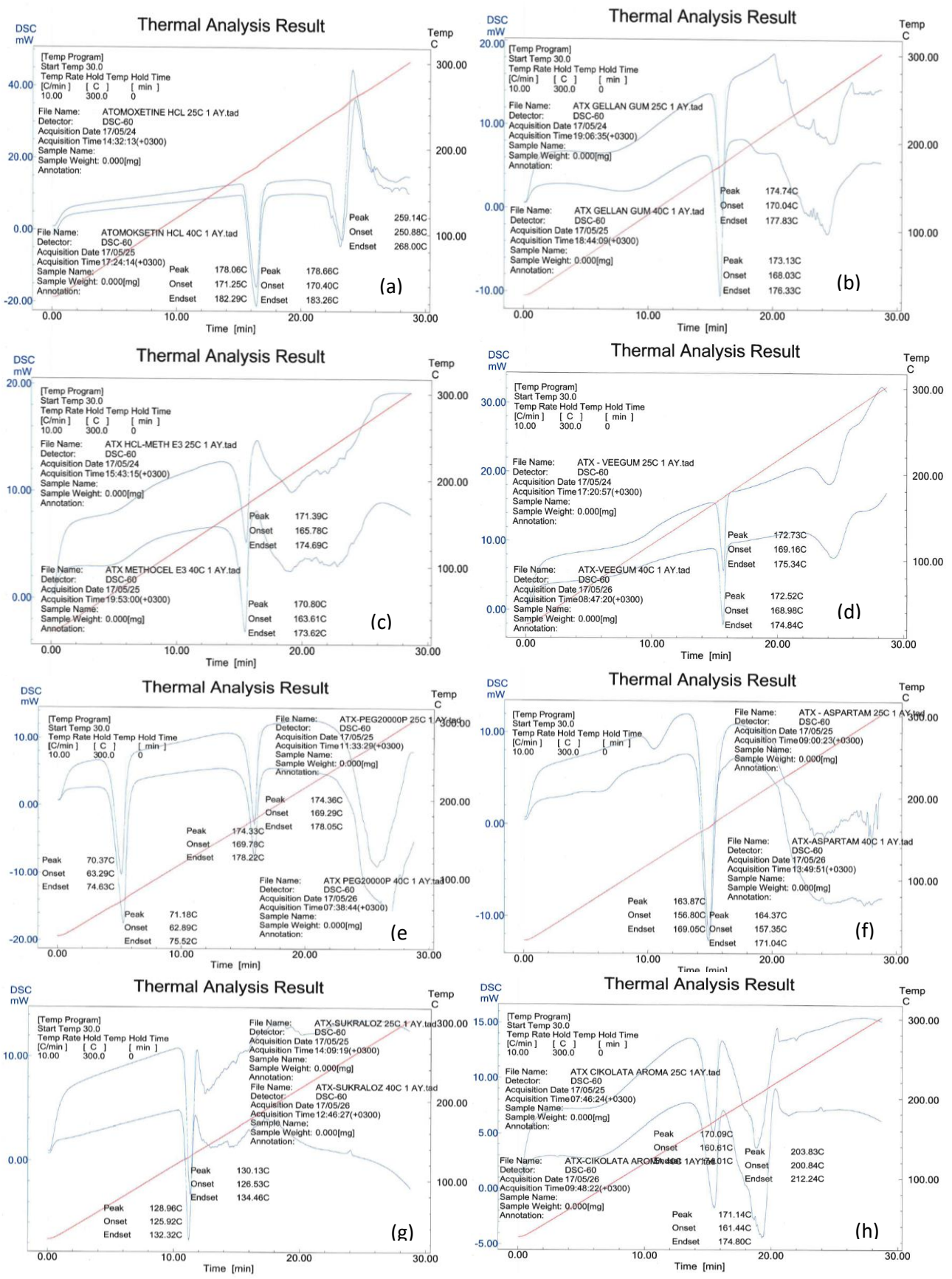

Figure 1. DSC compatibility studies.

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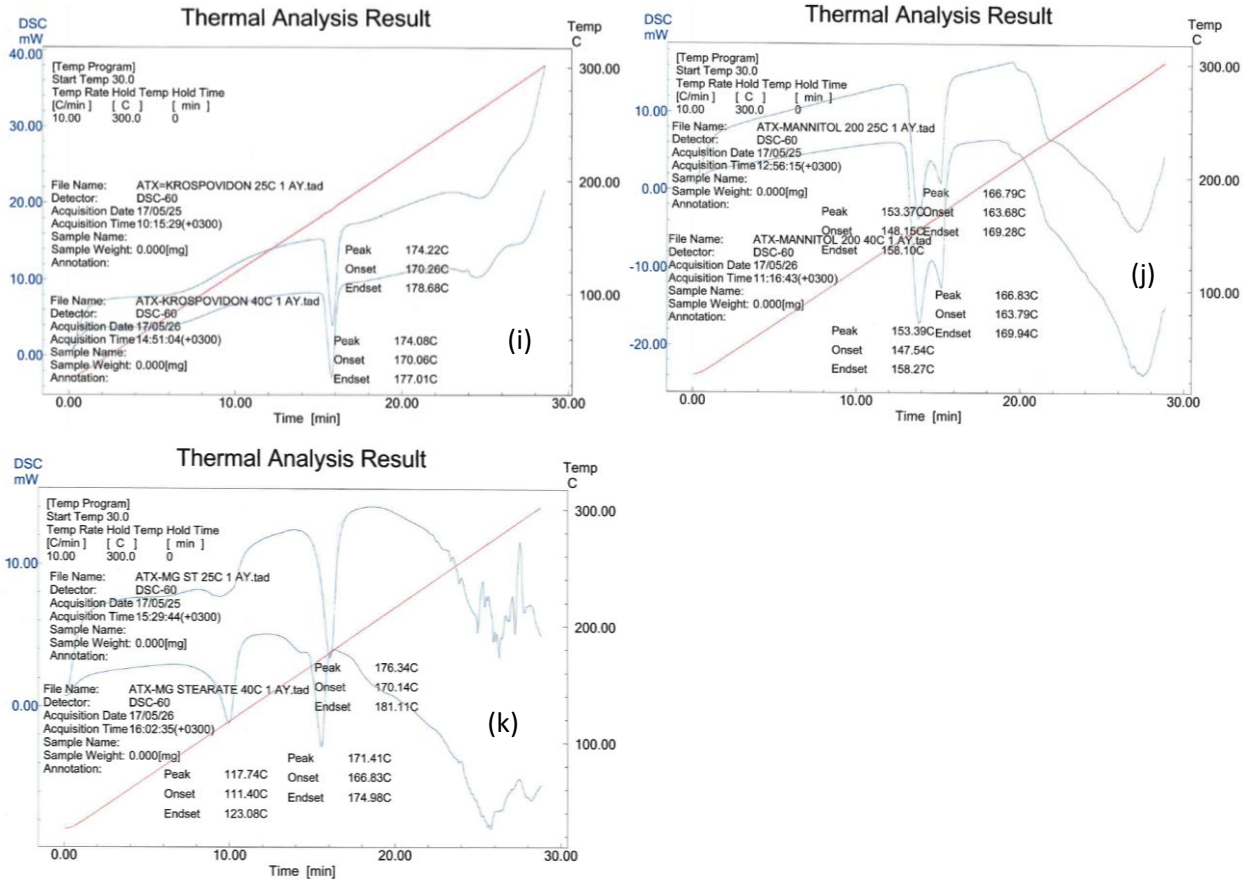

Figure 2. DSC compatibility studies (continued)(a) Atomoxetine HCl 25± 2°C, 60 ± 5% RH and 40± 2°C, 75± 5% RH for one month in glass bottles.(b) Atomoxetine HCl : Gellan Gum (1:1) 25± 2°C, 60 ± 5% RH and 40± 2°C, 75± 5% RH for one month in glass bottles.(c) Atomoxetine HCl : Methocel E3 (1:1) 25± 2°C, 60 ± 5% RH and 40± 2°C, 75± 5% RH for one month in glass bottles.(d) Atomoxetine HCl : Veegum (1:1) 25± 2°C, 60 ± 5% RH and 40± 2°C, 75± 5% RH for one month in glass bottles.(e) Atomoxetine HCl : PEG20000P (1:1) 25± 2°C, 60 ± 5% RH and 40± 2°C, 75± 5% RH for one month in glass bottles.(f) Atomoxetine HCl : Aspartame (1:1) 25± 2°C, 60 ± 5% RH and 40± 2°C, 75± 5% RH for one month in glass bottles.(g) Atomoxetine HCl : Sucralose (1:1) 25± 2°C, 60 ± 5% RH and 40± 2°C, 75± 5% RH for one month in glass bottles. (h) Atomoxetine HCl : White Chocolate Flavouring (1:1) 25± 2°C, 60 ± 5% RH and 40± 2°C, 75± 5% RH for one month in glass bottles. (i) Atomoxetine HCl : Crospovidone (1:1) 25± 2°C, 60 ± 5% RH and 40± 2°C, 75± 5% RH for one month in glass bottles. (j) Atomoxetine HCl : Mannitol 200 (1:1) 25± 2°C, 60 ± 5% RH and 40± 2°C, 75± 5% RH for one month in glass bottles. (k) Atomoxetine HCl : Mg stearate (1:1) 25± 2°C, 60 ± 5% RH and 40± 2°C, 75± 5% RH for one month in glass bottles.

The wetting time of formulations F01-F13 varied between 17 and 480 seconds and this period was shorter in trials using Veegum and PEG20000P as a binder-taste masking agent than in others. In parallel, in an evaluation of water absorption percentages, it was observed that the percentage of water absorption was higher in the experiments using Gellan gum than in others, which may be due to the instantaneous swelling characteristics of gellan gum when it comes in contact with water [26]. The percentage of water absorption decreased as the concentration of the binder-taste masking agent increased. When the disintegration time of the orally disintegrating tablets in purified water and a pH 6.8 phosphate buffer were examined, the disintegration time was found to be prolonged as the concentrations of the binder-taste masking agent increased, while no change was observed in the formulation which has Veegum. The disintegration time of the orally disintegrating tablets ranged from 5-60 seconds in purified water and from 5-59 seconds in a pH 6.8 phosphate buffer. These values fall within the European Pharmacopoeia specifications (180 seconds). In formulations F01-F13 of the orally disintegrating tablets, the loss of drying values, measured for information purposes, were found to be between 1.66 and 5.86%. Atomoxetine HCl is not sensitive to humidity, however, high levels of tablet moisture can affect tablet strength and friability in long-term stability.

Table 1. Taste-masked Atomoxetine HCl ODTs (formulations F01-F13).

Batch Number	F01	F02	F03	F04	F05	F06	F07	F08	F09	F10	F11	F12	F13
Batch Formula							mg/tablet						
Internal Phase													
Atomoxetine HCl[a]	11.43	11.43	11.43	11.43	11.43	11.43	11.43	11.43	11.43	11.43	11.43	11.43	11.43
HPMC (Methocel E3)	22.86	34.29	45.72	-	-	-	-	-	-	-	-	-	-
Gellan gum	-	-	-	22.86	34.29	45.72	-	-	-	-	-	-	-
Veegum	-	-	-	-	-	-	22.86	34.29	45.72	7.62	-	-	-
PEG20000P	-	-	-	-	-	-	-	-	-	-	22.86	34.29	45.72
Crospovidone-I	6.00	6.00	6.00	6.00	6.00	6.00	6.00	6.00	6.00	6.00	6.00	6.00	6.00
Ethanol (96%)[b]	q.s[c]	q.s[c]	q.s[c]	q.s[c]	q.s[c]	q.s[c]	q.s[c]	q.s[c]	q.s[c]	q.s[c]	q.s[c]	q.s[c]	q.s[c]
External Phase													
Veegum	-	-	-	-	-	-	-	-	-	15.24	-	-	-
Crospovidone-II	6.00	6.00	6.00	6.00	6.00	6.00	6.00	6.00	6.00	9.00	6.00	6.00	6.00
Mannitol 200	70.41	58.98	47.55	70.41	58.98	47.55	70.41	58.98	47.55	67.40	71.01	58.58	48.15
Flavouring	0.30	0.30	0.30	0.30	0.30	0.30	0.30	0.30	0.30	0.30	0.30	0.30	0.30
Aspartame	1.80	1.80	1.80	1.80	1.80	1.80	1.80	1.80	1.80	1.80	-	-	-
Sucralose	-	-	-	-	-	-	-	-	-	-	1.20	1.20	1.20
Mg Stearate	1.20	1.20	1.20	1.20	1.20	1.20	1.20	1.20	1.20	1.20	1.20	1.20	1.20
Tablet Weight	120.00	120.00	120.00	120.00	120.00	120.00	120.00	120.00	120.00	120.00	120.00	120.00	120.00

[a] Atomoxetine hydrochloride equivalent to 10 mg of atomoxetine.
[b] Vaporised during drying process.
[c] q.s: quantity sufficient.

Table 2. Results of the powder mixture analysis of formulations F01-F13.

Analysis	Bulk Density (g/ml)	Tapped Density (g/ml)	Carr Index (%)	Hausner Ratio	Angle of Repose (°)
Batch			Results		
F01	0.46	0.52	11.91	1.12	25°
F02	0.46	0.52	12.50	1.12	26°
F03	0.47	0.54	14.29	1.14	28°
F04	0.45	0.55	20.00	1.20	33°
F05	0.46	0.55	20.00	1.20	33°
F06	0.48	0.57	19.04	1.19	33°
F07	0.57	0.64	11.12	1.11	25°
F08	0.57	0.68	19.06	1.19	32°
F09	0.56	0.70	25.00	1.25	39°
F10	0.54	0.61	13.63	1.14	27°
F11	0.45	0.50	11.11	1.11	25°
F12	0.46	0.52	12.00	1.14	25°
F13	0.47	0.53	11.99	1.14	25°

The dissolution tests were performed, and the results were compared with the reference product (Tables 5 and 6). Strattera 10 mg Capsules (batch: C685992) were used as a reference product for comparison because atomoxetine HCl has no orally disintegrating form on the market. The assays for F01-F06 and F11-F13 were found to provide more than 85% dissolution in the 0.1 N HCl dissolution medium at 15 minutes, therefore, the dissolution rate profiles are considered similar without any mathematical calculations [27]. In formulations which contain hydroxypropylmethylcellulose (Methocel E3), the disintegration time increases when hydroxypropylmethylcellulose concentrations increase. However, in formulations F01-F03, this did not cause a significant change in the dissolution rate. Increasing the Gellan gum concentrations in formulations F04-F06 resulted in a decrease in the initial time points in the dissolution rate results in F04-F06. Thus, as stated in the literature, increasing the amount in the internal granular phase increases the duration of active substance release [28]. Formulations using PEG20000P as a binder-taste masking agent showed an increase in the dissolution rate results despite the prolonged disintegration time occurring with increasing concentrations of PEG20000P in F11-F13. It has been shown that hydrophilicity and solubility in water increases as the molecular weight increases in polyethylene glycols. Moreover, the solubility-enhancing effect of PEG20000P (used in the formulations) increases as concentrations increase as noted in the literature [29]. The release rate of F07-F10 in formulations using Veegum as a binder-taste masking agent showed that the release of active substances was low even at the 75-minute time point. Accordingly, a mathematical f2 similarity factor analysis was performed and the f2 results were found to be below 50, which can be attributed to the delay of the release of the active substance due to the adsorption effect of Veegum [30]. The results of the formulation studies and reference product are given in Figure 3.

When the assay analysis results of the formulations were compared with those of the reference product (Table 4), the results of F01-F06 and F11-F13 were found to be within the limits of "9.0-11.0 mg atomoxetine/tablet". However, these were out of the acceptable limits in formulations F07-F10.

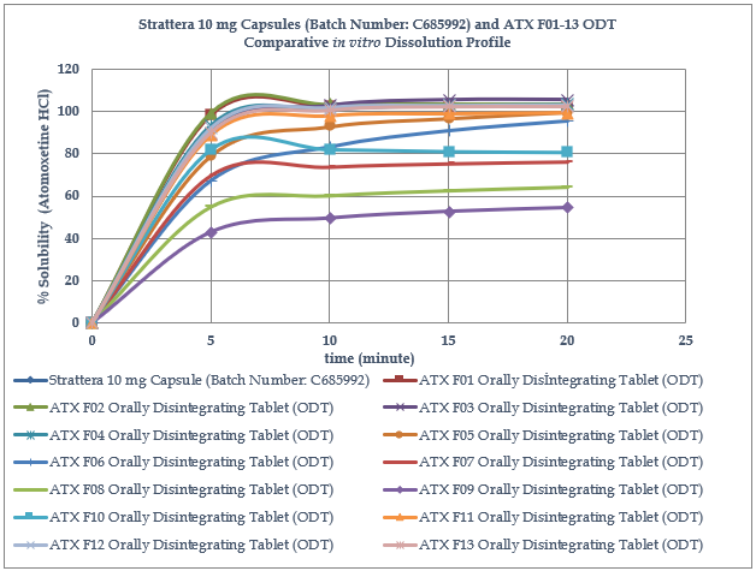

Figure 3. Comparative *in vitro* dissolution profile of the reference product and ODT formulations (F01-F13).

Table 3. Comparative physical analysis of formulations F01-F13 and the reference product.

Analysis	*Mean Weight (mg) ±SD[a]*	*Thickness (mm) ±SD[a]*	*Hardness (kp) ±SD[a]*	*Friability (%)*	*Wet. time (s) ±SD[a]*	*Water Absorb. Ratio (%) ±SD[a]*	*DT[b] Purified Water (seconds) ±SD[a]*	*DT[b], pH 6.8 phosphate buffer (seconds) ±SD[a]*	*Loss on Drying (%) ±SD[a]*
Batch					**Results**				
F01	121.3±0.82	2.42±0.01	2.37±0.05	0.25	127±0.52	61.4±2.44	6±0.52	7±0.52	2.50±0.04
F02	121.0±1.06	2.40±0.01	2.38±0.05	0.61	265±0.64	30.8±1.05	8±0.55	10±0.55	2.81±0.06
F03	120.5±0.81	2.41±0.01	2.42±0.04	0.59	480±4.06	14.7±1.17	22±0.53	11±0.55	3.09±0.21
F04	119.8±1.33	2.37±0.02	2.41±0.02	0.79	46±0.47	242.0±1.03	12±0.42	12±0.41	3.78±0.31
F05	120.5±0.77	2.29±0.01	2.35±0.03	0.99	138±0.71	156.1±2.14	23±0.52	32±0.51	4.73±0.25
F06	120.8±0.90	2.28±0.01	2.41±0.01	1.12	300±4.01	36.8±1.52	60±0.52	59±0.52	5.86±0.15
F07	120.9±1.01	2.35±0.01	2.38±0.03	0.33	18±0.51	99.7±1.38	5±0.81	6±0.82	2.38±0.07
F08	121.4±1.09	2.30±0.01	2.39±0.02	0.33	20±0.97	100.0±1.41	5±0.82	7±0.81	2.66±0.25
F09	120.8±0.92	2.24±0.01	2.42±0.01	0.25	17±1.03	108.7±1.03	6±0.52	7±0.53	3.08±0.31
F10	120.7±0.97	2.32±0.01	2.41±0.01	0.80	17±1.01	99.1±1.22	5±0.51	5±0.52	3.06±0.31
F11	120.2±0.85	2.41±0.01	2.42±0.02	0.20	34±1.94	82.0±1.15	6±0.55	9±0.52	1.68±0.11
F12	120.2±0.97	2.41±0.01	2.40±0.02	0.17	64±1.91	95.0±1.55	10±0.55	16±0.52	1.67±0.11
F13	119.9±0.93	2.39±0.02	2.41±0.02	0.12	169±2.56	40.0±1.37	19±0.56	47±0.57	1.66±0.12
Strattera 10 mg Capsules	278.8±0.33	-	-	-	-	-	360±2.82	300±2.90	7.18±0.10

[a] SD: Standard Deviation.
[b] DT: Disintegration time.

The impurity test results of the formulation and reference product were compared (Table 4), in which all results of formulation F04-F06 and F11-F13 trials were found to be within limits. However, the single impurity test results of formulations F01-F03 and F07-F09 were out of limits (above 0.2%).

According to the *in vitro* taste test results using an electronic tongue; in PCA graphs, PCA variance values contribute to the differentiation of the samples. The x-axis (PC1) represents the dominant variance that shows the significance in discrimination. The lower the variance value, the lower the discrimination of the Euclidean distance. The y-axis (PC2) is orthogonal and explains residual variation [31, 32]. Gellan gum, Veegum and Methocel E3 used in the formulations have PC1 test variance values of 71,121%, 76,715% and 75,879%, respectively, from which it can be concluded that samples have an accurately calculated Euclidean distance (Figures 4, 5 and 7). In contrast, the PC1 variance value was 53.879% in the formulations using PEG20000P, for which the difference between samples was not fully described (Figure 6). Sucralose solutions in PCA graphs contribute to inconsistent results, therefore the efficiency of taste masking is mainly assessed on the basis of the Euclidean distance between points corresponding to pharmaceutical formulations, their placebos and bitter active substance on the PCA plot [33].

Gellan gum formulations (F04-F06) and Veegum formulations (F07-F10) have shorter distances between their placebos and are more similar to their placebos (Figures 4 and 5).

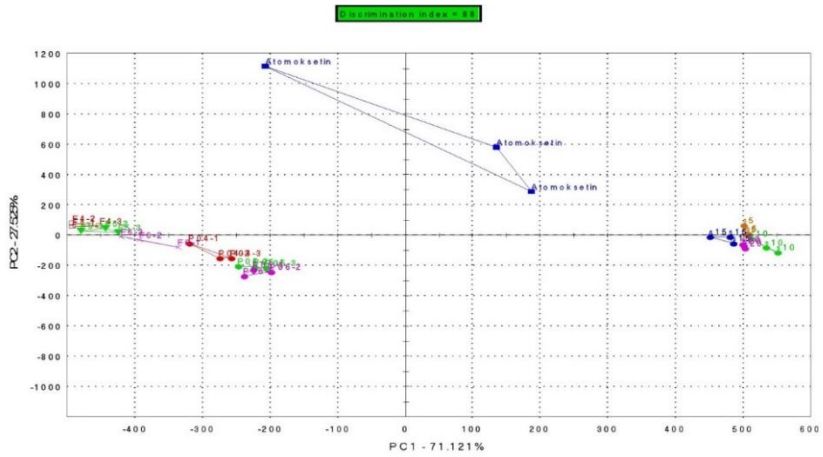

Figure 4. Comparative PCA graph of F04-F06, placebos (P04-P06), Atomoxetine HCl and sucralose solution (5%, 10%, 15% w/w).

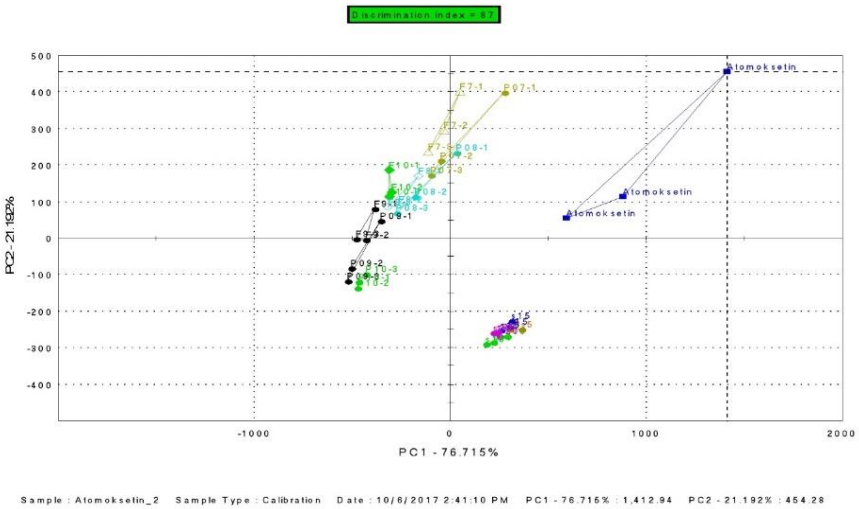

Figure 5. Comparative PCA graph of F07-F10, placebos (P07-P10), Atomoxetine HCl and sucralose solution (5%, 10%, 15% w/w).

In the Veegum formulations, many of the similarities were identified with the placebo rather than the formulations which contain Gellan gum, which may be due to its high adsorbent effect. However, in PCA graphs, formulations which have fewer similarities and a long distance between their placebo are respectively formulations using PEG20000P (F11-F13) and formulations using hydroxypropylmethylcellulose (Methocel E3) (F01-F03) (Figures 6 and 7). According to the results, taste masking could be achieved by using Gellan gum and Veegum in formulations.

3. CONCLUSION

This study presents the findings of experiments conducted in the masking of the taste of orally disintegrating tablets as an alternative to the reference product in capsule form. The results of physical (hardness, disintegration time) and chemical analyses (dissolution rate, determination of related substances, etc.) of the ODTs in formulations F04 and F12 were comparable with the reference product. In addition, *in vitro* taste test studies revealed that the bitter taste of the active substance could be masked by using the wet granulation method when the Gellan gum formulations were used as a taste masking agent, including F04. Additional studies using Gellan gum to prevent the reduction of tablet hardness in long-term stability, without affecting the disintegration time, dissolution rate or *in vitro* taste behaviour, may be feasible. The data obtained in this study provided additional information to the literature for future taste masking studies using atomoxetine HCl in dosage forms that can be administered orally.According to this data, it is possible to say that Gellan gum has a taste masking effect on orally disintegrating tablet formulations which contain atomoxetine HCl.

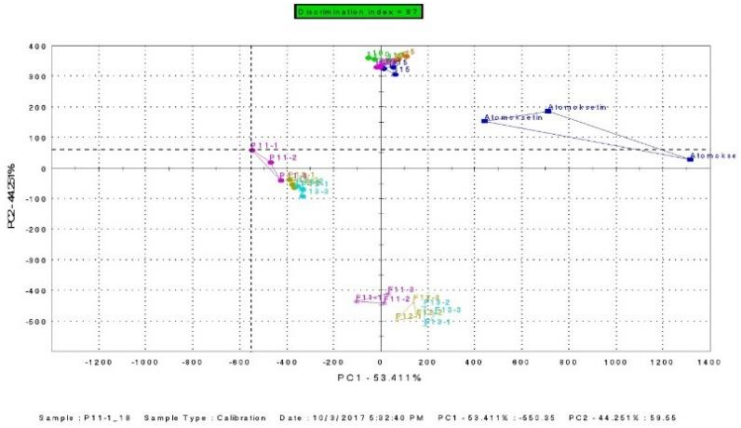

Figure 6. Comparative PCA graph of F11-F13, placebos (P11-P13), Atomoxetine HCl and sucralose solution (5%, 10%, 15% w/w).

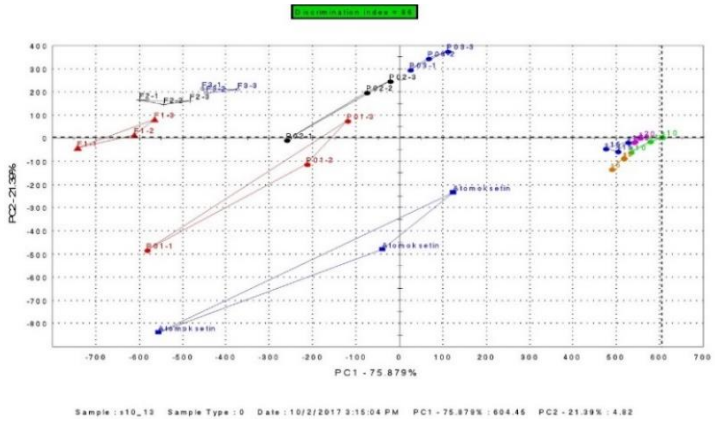

Figure 7. Comparative PCA graph of F01-F03, placebos (P01-P03), Atomoxetine HCl and sucralose solution (5%, 10%, 15% w/w).

Table 4. Comparative chemical analysis (assay and related substances) of formulations F01-F13 and the reference product.

Analysis	***Assay***	***Impurity***			
Specification (Anticipated)	*9.0-11.0 mg Atomoxetine/Tablet (90.0-110.0%)*	*Impurity Limits: Desmethyl Atomoxetine max. 0.3%, Atomoxetine N-amide max. 0.2%, Unknown Single Impurity max. 0.2% and Total Impurity max. 1.0%.*			
		Results			
Batch	mg/tablet[a]	Desmethyl Atomoxetine	Atomoxetine N-amide	Unknown Single Impurity	Total Impurity
F01	9.79±0.59	0.01	[b]	0.16	0.21
F02	10.10±2.02	0.01	[b]	0.29	0.32
F03	10.23±0.98	0.01	[b]	0.26	0.28
F04	9.62±2.04	0.01	[b]	0.04	0.08
F05	9.62±1.06	0.01	[b]	0.09	0.12
F06	9.40±1.05	0.01	[b]	0.10	0.14
F07	8.36±1.11	0.01	[b]	0.55	0.58
F08	7.81±2.27	0.01	[b]	0.28	0.31
F09	7.64±2.20	0.01	[b]	0.32	0.36
F10	7.68±2.24	0.01	[b]	0.06	0.08
F11	9.64±2.70	0.01	[b]	0.08	0.12
F12	9.65±2.13	0.01	[b]	0.08	0.12
F13	9.43±1.82	0.01	[b]	0.06	0.15
Strattera 10 mg Capsule	10.13±2.03	0.06	[b]	0.06	0.08

[a] Assay results are represented as mean±standard deviation (SD).
[b] Under the identification threshold limit.

4. MATERIALS AND METHODS

4.1. Materials

Atomoxetine Hydrochloride (ATX, Hetero Drugs Ltd., India), excipients; HPMC E3 (Methocel E3, Colorcon), Gellan gum (Pfannenschmidt, Germany), Veegum (Vanderbilt Minerals LLC, USA) PEG 20000P (Clariant), Mannitol 200 (Parteck M 200, Merck) Crospovidone (Polyplasdone, Ashland), White chocolate flavouring (Firmenich), Aspartame (Ajinomoto Group), Sucralose (Ji An Newtrend Tech), Magnesium stearate (Faci), Ethanol (96%) (Merck). All other used chemicals were of analytical grade.

4.2. Methods

4.2.1. Active substance and excipient compatibility studies

The active substance was mixed with the chosen excipients at a ratio of 1:1 and filled into glass bottles. The mixtures were placed in stability cabinets for 1 month at both 25 ±2°C 60 ±5% RH and 40 ±2°C 75 ±5% RH conditions. At the end of the period, the samples were analysed by differential scanning calorimetry (DSC-Shimadzu) and the compatibility between the active substance and the excipients was evaluated.

4.2.2. Preparation of orally disintegrating tablets (ODTs) containing atomoxetine HCl

The present studies employ a wet granulation method to mask the taste of the active ingredients. The natural polymers Veegum and Gellan gum, can exhibit both binding and taste masking properties for use in granulation, and Hydroxypropylmethyl cellulose (Methocel E3) and Polyethyleneglycol 20000P were selected as synthetic polymers. The dispersion properties of Veegum and Gellan gum have been documented in the literature [28, 30]. Since the taste of the active ingredient is quite bitter, flavourings (white chocolate) and sweeteners (aspartame, sucralose) were added to the formulation. To determine the taste masking effect, three different active substance/polymer ratios of 1:2, 1:3 and 1:4 were investigated for each polymer in the studies.

Atomoxetine HCl, a binder-taste masking polymer (Hydroxypropylmethylcellulose (Methocel E3), Gellan gum or Veegum) and Crospovidone-I were passed through an 841-micron sieve. The sieved substances were placed in a wet granulator and mixed for 5 minutes. Ethanol (96%) was added to the powder mixture until wet granulation was achieved. The wet granules were passed through an 841-micron sieve and dried in an oven at 50± 5°C for about 1 hour. The dry granules and Mannitol 200, Crospovidone-II, Aspartame (or Sucralose) and White Chocolate Flavouring were blended and sieved through an 841-micron sieve. The sieved powder mixture was mixed in a cubic mixer for 10 minutes at 12 rpm. Magnesium Stearate was then passed through a 420-micron sieve and added to the powder mixture and stirred at 12 rpm for 3 minutes, and the tablets were compressed with 8 mm round punches.

4.2.3. Evaluation of powder properties

Powder properties of the final mixture were analysed before tablet compression.

Angle of Repose: In each study, the powder mixture weighed at 50 grams was passed through a hopper onto a flat surface and the angle of repose was measured. If the angle of repose was less than 30°, the powder could flow freely [34].

Bulk Density and Tapped Density: The powder mixture prepared for each formulation was filled into a 100-mL graduated cylinder and the powder volume and the weight obtained were recorded. Then, with the help of a tapped density device (Erweka), the tapped volume was measured and the tapped density (Td) was calculated [34].

Carr Index (Compressibility %) and Hausner Ratio: Carr index and Hausner ratio were calculated. If the Hausner ratio of the powders was less than 1.25, that meant the powder had good flow properties and if the Hausner ratio was more than 1.25, that meant the powder had poor flow properties [35].

4.2.4. Evaluation of orally disintegrating tablets

Average Weight and Weight Uniformity: 20 tablets of each formulation were weighed, and the mean weight values were calculated and recorded.

Thickness: The thickness of 10 tablets from each formulation were measured by using the compass (Mitutoyo Corp.).

Hardness: The hardness of the 10 tablets from each formulation was measured with a hardness tester (Erweka).

Friability: 20 tablets of each formulation were weighed and placed in a friabilitor (Distek), then rotated at 25 rpm for 4 minutes.

Wetting Time and Water Absorption %: A piece of pelure paper was cut in a circular shape and placed in a petri dish. 6 mL of deionised water was poured onto the pelure paper. A tablet was carefully placed on the surface of the tissue paper and the time required for complete wetting was measured. Then the wetted tablet was reweighed. Water absorption ratio, R is determined using the following Equation 1. For each formulation 6 tablets were used for the study.

$$R\ (\%\ \text{Water absorption}) = 100 \times (Wa - Wb) / Wb \qquad \text{(Eq. 1)}$$

Where, Wb is the weight of the tablet before water absorption and Wa is the weight of the tablet after water absorption [25].

Disintegration Time (DT): The disintegration time of 6 tablets was measured in 1000 mL of purified water at 37ºC using a disintegration test apparatus. In addition, due to its similarity to the pH of saliva, the disintegration test was also performed with 1000 mL of a pH 6.8 phosphate buffer.

Loss on Drying: The loss on drying analysis for each tablet powder was performed with a halogen moisture analyzer using a thermogravimetric method. 2 g of powder sample was heated through absorption of IR radiation from a halogen radiator to 105ºC. A further measuring method was continual determination of mass during the drying process. The moisture content percentage was determined from the difference in weight before and after drying.

Dissolution Test (Profile): In US Pharmacopoeia (USP 39), the dissolution tests indicated for the capsule form were adapted to the ODTs [36]. The analysis was performed at 50 rpm (Method II) in a 1000-mL 0,1 N HCl dissolution medium (37 ± 0.5°C). The samples were collected at time intervals of 5, 10, 15 and 20 minutes, and analysed by RP-HPLC (Shimadzu). For each formulation, 12 tablets were used for the *in vitro* dissolution profile (Table 5 and 6).

Assay and Related Substances Analysis: In US Pharmacopoeia (USP 39), the assay test and related substances analysis of atomoxetine indicated for the capsule form and the methods were adapted to the ODTs [36]. For each formulation, 4 tablets were used in the assay and 3 tablets were used for the related substances analysis with three replicates. The Assay and Related substances analysis were performed using a RP-HPLC analysis recommended in pharmacopoeia.

Impurity Limits for Atomoxetine Capsules in US Pharmacopoeia (USP 39): *Desmethyl Atomoxetine max. 0.3%, Atomoxetine N-amide max. 0.2%, Unknown Single Impurity max. 0.2% and Total Impurity max. 1.0%*. These limits were used for this study.

In Vitro Taste Analyzer: An *in vitro* analysis of taste masking from tablets of each experiment was performed using an Astree electronic tongue (E-tongue).

Sample preparation & Analysis: ODT formulations F01-F13, their placebo powders, the active ingredient Atomoxetine HCl and Sucralose solutions were prepared. Due to its sweet taste, sucralose solutions with different concentrations were included for information purposes and comparison. Atomoxetine HCl was weighed at 11.43 mg as in ODT formulations. Placebo powders were prepared separately according to the tablet formulations and then weighed at 108.57 mg. F01-F13 tablets were weighed directly. Each sample was transferred into a volumetric flask by adding 100 mL of deionized water. Each sample was diluted for 15 minutes under magnetic stirring. The mixtures were filtered with filter paper and then, transferred into 25 mL-beakers. Sucralose solutions at concentrations of 5%, 10%, 15% and 20% were poured directly into 25 mL-beakers. Each sample was tested on an Astree e-tongue at least 3 times with three replicates for each sample for the statistical analysis. The average values between 100 and 120 s were used to build the maps. Astree sensors were cleaned in deionized water between each sample measurement.

The assays were realized on an Astree e-tongue system equipped with an Alpha M.O.S. sensor set (for pharmaceutical analysis) composed of 7 sets of sensors (ZZ, AB, BA, BB, CA, DA, JE) on a 16-position autosampler using 25 mL-beakers. Sampling times were fixed at 120 s. All the data generated on the Astree system were processed using multidimensional statistics on AlphaSoft V12.3 software. The working principles of the sensors are based on the electrochemical potentiometric sensor technology CHEMFET (Chemical Modified Field Effect Transistor). Each sensor is sensitive to the substances in the samples and converts the response to the signals to be analysed. The detection method is based on measuring the voltage difference between the CHEMFET sensor and the Ag/AgCl reference electrode. Statistical methods such as basic

component analysis (PCA) and differential factor analysis (CFA) are used in the data processing [37, 38]. The PCA allows the data obtained by all seven sensors to be used to differentiate between samples on a two-dimensional graph which represents the two principal components. The axis containing the most amount of variance is shown as the first principal component (PC1), and the following axis is the second principal component (PC2), etc. In the PCA maps, data points of the samples are compared using the calculated distance between them. The distance between each tablet formulation and placebo (Euclidean distance) is determined to evaluate taste differences and similarities. The shorter this distance, the smaller the difference in taste. In the evaluation of taste masking, the lower the distance between the placebo and the drug formulation, the more effective the taste masking is [31, 39, 40]. To investigate a better correlation between e-Tongue data and the actual bitterness, the sensors used for the PCA were optimized. The six types of sensors, ZZ, AB, BA, BB, CA and DA were ultimately selected as best suited to the bitterness evaluation.

Table 5. Comparative *in vitro* dissolution profile of the reference product and formulations F01-F06.

Batch / *minute*	*Strattera 10 mg Capsule*	*F01*	*F02*	*F03*	*F04*	*F05*	*F06*
				% Solubility[a]			
5	91.0±7.43	98.1±3.17	99.2±2.02	89.7±3.64	93.4±3.41	79.1±4.47	67.4±3.82
10	101.3±3.06	102.4±2.46	103.1±2.08	102.9±1.79	100.8±3.94	92.9±3.76	83.3±3.94
15	102.7±1.68	102.5±2.61	103.3±2.16	105.6±2.34	102.7±4.46	96.8±3.57	91.0±3.42
20	102.6±2.69	102.3±2.63	103.3±2.17	105.7±2.31	103.1±4.68	99.8±3.53	95.6±3.42
f2	-	[b]	[b]	[b]	[b]	[b]	[b]

[a] Solubility results are represented as mean±standard deviation (SD).
[b] More than 85% of the drug is dissolved within 15 minutes; dissolution profiles may be accepted as similar without further mathematical evaluation.

Table 6. Comparative *in vitro* dissolution profile of the reference product and formulations F07-F13.

Batch / *minutes*	*Strattera 10 mg Capsules*	*F07*	*F08*	*F09*	*F10*	*F11*	*F12*	*F13*
					% Solubility[a]			
5	91.0±7.43	69.8±3.31	55.0±3.53	42.9±3.08	81.9±3.12	88.8±3.24	92.1±3.33	90.2±3.31
10	101.3±3.06	73.8±2.77	60.3±3.00	49.5±2.54	81.9±2.92	97.9±3.67	101.8±4.43	100.6±2.63
15	102.7±1.68	75.4±2.63	62.7±2.70	52.6±2.12	80.9±2.84	98.8±3.57	102.7±4.80	102.2±2.73
20	102.6±2.69	76.3±2.41	64.4±2.11	54.4±2.23	80.6±2.83	99.3±3.78	102.9±4.87	102.3±2.74
f2	-	***30.7***	***22.6***	***17.4***	***33.9***	[b]	[b]	[b]

[a] Solubility results are represented as mean±standard deviation (SD).
[b] More than 85% of the drug is dissolved within 15 minutesİ dissolution profiles may be accepted as similar without further mathematical evaluation.

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