Orally Disintegrating Tablets of Cinnarizine and Domperidone: A New Arsenal for the Management of Motion Sickness

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ABSTRACT

Cinnarazine and Domperidone are antiemetic drugs used in the treatment of motion sickness. These drugs are currently available in a combination form as conventional tablets for oral administration. Combination of Cinnarizine and Domperidone is ideal for the management of motion sickness. However, the conventional tablets need to be taken 1-2 hours before travel and 1 tablet every 6 hours during journey which results in a patient non-compliance specially for pediatric and geriatric population and the onset of action is slow. Orally disintegrating tablets (ODTs) provide quick relief from motion sickness due to rapid onset of action, ease in swallowing and better compliance. Hence, the aim of this study was to prepare ODTs of Cinnarazine and Domperidone by direct compression method. The tablets were prepared using Pearlitol200SD and microcrystalline cellulose pH102 as diluents and aspartame as sweetening agent along with three different levels of superdisintegrants namely CrospovidoneXL, Croscarmellose sodium (Ac-di-sol) and Sodium Starch Glycolate which were employed in the range of 2.5-5%, 1- 5% and 4-8% respectively. The tablets were evaluated for content uniformity, drug content, hardness, friability, wetting time, disintegration time and dissolution. All the nine batches formulated showed a disintegration time of less than 30 seconds.

Keywords:

Cinnarizine, domperidone, disintegration time, direct compression, ODTs, superdisintegrant

1. Introduction

Oral route is the most convenient and commonly employed route of drug delivery due to its distinct advantages like ease of manufacture,

ease of administration, cost effectiveness, patient compliance, safety, effectiveness, etc. However, paediatric and geriatric populations have difficulties in swallowing tablets and capsules. Moreover conventional tablets have a slower onset of action and require water for swallowing.This results in non-compliance to the prescription resulting in high incidences of ineffective therapy. 'Orange Book' of the USFDA defines Orally Disintegrating Tablets (ODT) as "A solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue [1]". European Pharmacopoeia adopted the term "Orodispersible tablet" and described orally disintegrating tablets as "uncoated tablets intended to be placed in the mouth where they disperse rapidly before beingswallowed" and as tablets which should disintegrate within 3 min.

Such ODTs, form a dispersion of drug in the saliva which moves down the GI tract alongwith the salivary movement and minute amount of saliva is sufficient which obviates the need of water. Geriatric, pediatric and traveling patients who may not have ready access to water are benefitted by such dosage forms. ODTs have all the advantages of solid

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dosage forms, such as good stability, accurate dosing, easy manufacturing, small packaging size, and easy handling by patients. ODTs also have the advantages of liquid formulations, such as easy administration and no risk of suffocation resulting from physical obstruction by a dosage form [2].

Motion sickness is the uncomfortable dizziness, nausea, and vomiting that people experience when their sense of balance and equilibrium is disturbed by constant motion. Riding in a car, aboard a ship or boat, or riding on a swing all cause stimulation of the vestibular system and visual stimulation that often leads to discomfort. While motion sickness can be bothersome, it is not a serious illness, and can be prevented [3]. Domperidone (DOM) is a poorly water soluble dopamine D2 antagonist which speeds gastrointestinal peristalsis and is widely used as an antiemetic. Cinnarizine (CINN) is an anti-histaminic drug which binds to histamine receptors of vestibular nerves and is mainly used for the control of vomiting due to motion sickness. Combination of CINN and DOM is ideal for the management of vestibular disorders prophylaxis and control of motion sickness and nausea & vomiting of various aetiologies due to the synergistic action of DOM and CINN [3]. Conventional CINN and DOM combination tablets are available in the domestic as well as international market. But they suffer from distinct disadvantages like slower onset of action, requirement of water, patient non-compliance since the tablet has to be taken 1-2 hours before journey and the patient may miss the dose and difficulty in swallowing tablets by pediatric and geriatric patients. In order to circumvent such problems ODTs of the two drugs can be prepared. Thus the aim of the present paper was to formulate and evaluate ODTs of CINN and DOM.

2. Materials and Methods

2.1 ***Materials:*** CINN and DOM were obtained as gift samples from Zota Health Care, Surat, India

2.2. *Preformulation Studies*

Characterisation of API [4]

CINN and DOM were characterised in terms of organoleptic properties, melting point, solubility, assay, flow property, FTIR (Bruker Optics (ALPHA), Germany), and DSC (Shimadzu DSC-60,Shimadzu Corporation, Kyoto, Japan).

Drug-Excipient Compatibility Study

The compatibility of both drugs with formulation excipients was studied by placing the lubricated blend (A blend prepared by mixing APIs, Microcrystalline Cellulose pH102, Pearlitol200SD, CrospovidoneXL, Aerosil 200, Aspartame and Sodium Stearyl Fumarate- Batch1) in three different conditions like petridish, petridish with black cover and Alu pouches. All the samples were studied for physical and chemical changes.

Differential Scanning Calorimetry (DSC)

The thermographs of each API and its combination were obtained by using a Shimadzu DSC-60 differential scanning calorimeter. Samples accurately weighed (2–3 mg) were placed in pierced aluminium pans and heated from 20 to 260^0C at a scanning rate of 10^0C/min in a nitrogen atmosphere.

FTIR

Pure CINN and DOM were subjected to FTIR for determination of functional groups present in the structure. Appropriate quantities of samples were kept on a FTIR-ATR and spectrum was recorded.

Assay of API [4]

Assay of CINN and DOM was performed according to Indian Pharmacopoeia 2010 by titrimetric analysis.

Melting Point [5, 7]

Melting point of pure CINN and DOM were determined using capillary heating method.

2.3 ***Analytical Method Development*** [6, 15]
First derivative UV-VIS Spectrophotometry was used to develop analytical method for simultaneous estimation of CINN and DOM in tablets. Zero crossing points (ZCP) for 10 µg/ml solutions of each drug were determined by scanning the solution at 200-400nm. The first derivative absorbance of CINN was taken at the ZCP of DOM and vice versa in order to nullify the interference of one drug in the analysis of other.

2.4 ***Precompression Evaluation***
Flow property of the lubricated blend was performed in terms of Angle of Repose, Bulk density, Tapped density, Carrs Index and Haussner ratio.

2.5 ***Tablet Preparation*** [8-10]
CINN, DOM, Microcrystalline Cellulose pH102, Mannitol (Pearlitol200SD), Superdisintegrants (Crospovidone XL, Ac-di-sol SD711 and Sodium Starch Glycollate), Colloidal Silicon Dioxide (Aerosil200) and Aspartame were sifted through sieve no. 30 and blended in a plastic bag for 10 minutes. Sodium Stearyl Fumarate was passed through a sieve no. 60 and then blended with the initial mixture in the plastic bag for additional 2 minutes. The blend was then compressed on rotary tablet press (B tooling, Cadmach, India) using 8-mm diameter circular standard concave punches. Nine batches were prepared with a target mass of 200 mg (Formulations codes F1–F9). The composition of these formulations is shown in **Table 1.**

2.6 ***Evaluation of Tablets*** [4, 11, 12]

Weight Variation
Twenty tablets were selected at random, weighed and the average weight was calculated.

Hardness
Tablet hardness of each formulation was determined using a Monsanto hardness tester. Results were calculated from the average results of six tablets.

Thickness
Tablet thickness was determined using vernier callipers and average of six tablets was recorded.

Friability
For each formulations, preweighed tablet samples equivalent to 6.5 gm were placed on the Roche Friabilator, which was then operated for 100 revolutions. The tablets were then dusted and reweighed, % friability was calculated.

Disintegration test
Disintegration time was determined using USP tablet disintegration test apparatus using 900 ml of distilled water without disk at 37 ± 0.5° C temperature. An average Disintegration Time (D.T) of 6 tablets was recorded.

Wetting time
The wetting time of the tablets was measured using a simple procedure. Five
circular tissue papers of 10 cm diameter were placed in a petridish with a 10 cm diameter. Ten ml of water-containing 1% Amaranth, a water soluble dye, was added to petridish. A tablet was carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet was noted as the wetting time. An average of 3 tablets was recorded.

Assay
Total 10 tablets were accurately weighed, crushed and powder equivalent to 200mg was taken, dissolved in 100 ml, 0.1NHCl, sonicated for 10 mins and analysed for drug content using first derivative UV-VIS Spectrophotometry method. For DOM, the assay limits are 95-105% and for CINN, the assay limits are 90-110% according to IP2010.

Content Uniformity

10 tablets were crushed individually and the content of active ingredient in each tablet was estimated individually using the assay procedure.

In vitro drug release

In vitro drug release study was performed as per the following specifications:

- Apparatus: USP dissolution testing apparatus II (Paddle)
- Dissolution medium: 0.1 N HCl
- Volume of medium: 900 ml
- Speed of paddle: 50 RPM
- Temperature of medium: 37± 0.5 ^{0}C
- Sampling interval: 0, 2, 4, 6, 8, 10, 12, 15, 20, 30 min.
- Sampling volume: 10 ml

The volume withdrawn at each time interval was replaced with fresh dissolution medium of same quantity maintained at 37$\pm$0.5^{0}C. The samples were filtered through a 0.45µ membrane filter. Absorbance of these solutions was measured at 236nm for DOM and 254nm for CINN using a Shimadzu UV-1800 UV-visible double beam spectrophotometer. Percentage of drug release was calculated using an equation obtained from the standard curve.

2.7 *Comparison with marketed preparation*

STUGIL tablets (15mg DOM + 20mg CINN), Johnson and Johnson, were used for comparison of in-house batches with marketed preparation. All evaluation parameters were performed similarly for these tablets and results were recorded.

2.8 *Accelerated Stability study* [13]

The prepared in house tablets were subjected to short term stability study for a period of three months as per ICH guidelines. In the present study, stability studies were carried out at 40 ^{0}C/75% RH for a specific time period up to three months for optimized formulation.

2.9 *Photostability Study*

The prepared tablets were subjected to photostability study in aphotostability chamber Osworld JRIC-11B at 1.2 million lux hours for specified time interval as per ICH guidelines.

3. Results and discussion

3.1. *Preformulation studies*

Characterisation of API

The identification and characterisation of API was done in terms of organoleptic properties, melting point, saturation solubility, assay, flow properties, FTIR and DSC. The results are shown in **Table 2**.

The results showed that both the API were found to have poor flow property as determined by Hausner's ratio, compressibility index and angle of repose. The assay values of pure API as performed by titrimetric method showed results within the range as per IP'2010, which suggested that the API samples were pure and could be used for further processing.

FTIR

Figure 1 shows the FTIR spectrum of CINN. The spectrum of pure CINN shows an absorption band at 3065 cm^{-1} due to C-H stretching of aromatic compounds. Absorption band at 3021 cm^{-1} is due to =C-H stretch of alkenes. Bands between 2969-2806 cm^{-1} indicate the presence of aliphatic C-H groups. A strong absorption band at 2765 cm^{-1} shows the presence of N-H due to bending vibrations. Stretching at 1683-1635 cm^{-1} is due to –C=C- of alkenes. Sharp bands between 1447-1355 cm^{-1} reveal the presence of C-H of alkanes. This is in good correlation with the reported data of the drug.

Figure 2 shows the spectrum of DOM. The absorption bands in the range of 3024-2937 cm^{-1} are due to C-H stretch of aromatics. The bands in the range of 2817-2768 cm^{-1} are due to C-H stretching of alkanes. Sharp bands at 1038-1022 cm^{-1} and 1147-1125 cm^{-1} are due to C-N stretching which indicate the presence of –C-N-C- group in the structure. Bands at 1062-1102 cm^{-1} are due to C-O stretching. A strong band at 1147 cm^{-1} and 1125cm^{-1} is due

to C-H wagging which indicates presence of alkyl halides in the structure.

A band at 1622 cm^{-1} is due to bending of N-H which indicates the presence of –NH group in the structure. Bands at 900-675 cm^{-1} and 758-731 cm^{-1} show presence of aromatic ring in the structure. A band at 664 cm^{-1} is due to N-H wagging which reveals the presence of secondary amine. A band at 587-572 cm^{-1} is due to C-Cl stretch which indicates presence of Chloride group in the structure. The results are in good correlartion with the reported data of the drug.

DSC

Figure 3 shows the DSC curve of CINN. A sharp endothermic peak was obtained at 122^0C which indicated pure unprocessed CINN present in the crystalline form free from impurities.The recorded endothermic peak correlates with the reported melting range of CINN [12].

Figure 4 shows the DSC curve of DOM. A sharp endothermic peak was obtained at 250.8^0C which indicated pure unprocessed DOM present in crystalline form. The recorded endothermic peak correlates with reported melting range of DOM [12]. **Figure 5** shows DSC curve of physical mixture of DOM and CINN. The presence of sharp endothermic peaks at their respective melting points indicates that there is no interaction between the two drugs and the combination can be used for further processing.

Drug-excipient compatibility

Drug-excipient compatibility was checked and the results are showed in **Table 3**. The results showed that there was no change in physical, chemical parameters and DSC peaks of individual drugs after 1 month charging of samples in open petridish, covered petridish and alu pouches. It was inferred from the results that both drugs are compatible with the formulation excipients and thus could be safely used for formulating the tablets.

3.2 ***Precompression Evaluations***

Prior to compression, the powder blends were evaluated for the parameters referring to flowability and compression. **Table 4** shows the precompression parameters of the lubricated blends used in the compression of the tablets. It was inferred that the flow property was excellent which justified the use of direct compression technique for preparation of tablets. The use of granular grades of excipients like Pearlitol200SD and MCCpH102 and use of Aerosil200 which serves as a glidant justifies the obtained flow property [14].

3.3 ***Analytical Method Development***

Analytical method for the simultaneous estimation of both drugs in mixture as well as tablets was developed using first derivative UV-VIS spectrophotometry. The first derivative calibration curve for both the drugs are given in **Figure 6.**The linear plot obtained for both the drugs and r2 values approaching 1indicates the perfect correlation between first derivative absorbance and concentration.Thus the method developed could simultaneous estimation of two drugs in formulated tablets [15].

3.4 ***Evaluation of Tablets***

The post-compression parameters such as hardness, friability, thickness, tablet weight variation, disintegration time, wetting time are presented in **Table 5**.

Hardness

The hardness of 3-4 kg/cm2 indicated good mechanical strength with non-significant differences in all formulations.

Friability

Friability was less than 1 % for all batches which indicates that the batches showed good mechanical resistance.

Weight Variation

No significant weight variability was observed in the produced tablets.

Wetting Time

Wetting is closely related to inner structure of tablets and the hydrophilicity of excipients. Wetting time was determined to get idea of wetting lag time before disintegration. Results reveal that the conventional tablets STUGIL show higher wetting time (8-9 mins) compared to tablet prepared using Sodium starch glycolate, Croscarmellose sodium, and Crospovidone XL , as the concentration of disintegrant increased there was decrease in wetting time. This may be due to their ability of swelling and capacity to absorb water. The results of wetting time of ODT are in compliance with Reddy UV et al [11] who observed that as the concentration superdisintegrant increased there was decrease in wetting time.

Disintegration Time

As evident from the results, *in vitro* disintegration times decreased by increasing the amount of superdisintegrant in the tablet formulation. In case of CrospovidoneXL, as the amount of superdisintegrant increased, swelling action is enhanced, thus more water enters the formulation thus breaking the tablet apart at a faster pace. In batches with sodium starch glycollate, disintegration occurs by rapid uptake of water followed by rapid and enormous swelling. 5 % Ac-Di-Sol containing batch showed most rapid disintegration. Water wicking and swelling are the mechanisms of disintegrant action for Ac-Di-Sol. Exposure to water can cause ingredients to swell and exert pressure against surrounding tablet ingredients, causing existing bonds between particles to break. The fibrous nature of Ac-Di-Sol provides many sites for fluid uptake and gives it excellent water wicking capabilities. The cross-linked chemical structure of Ac-Di-Sol creates an insoluble, hydrophilic, and highly absorbent excipient that results in exceptional swelling properties [16]. In one way ANOVA followed by Tukey-Alpha Multiple Comparisons Test, P value of comparing batches was less than 0.05, which rejects the null hypothesis, thus proving that there is a significant difference between the DTs obtained. Drug content, Content Uniformity and *in-vitro* dissolution results are shown in **Table 6**.

Assay

The percentage drug content in lubricated blends and prepared tablets was found to be between 97.5 to 103.1 %, (Table 6).

Content Uniformity

Drug content was found to be consistent and uniform in all tablet formulations (> 98 %) (Table 6), which ensures the uniform distribution of the required dose in each of the tablets of all batches prepared.

***In vitro* dissolution**

In vitro dissolution of all batches is shown in the **Table 7 and Table 8**. Marketed-STUGIL tablets showed 46.4 ±1 .2% CINN and 21.6 ± 1.02% DOM after 6 mins while the in-house batches showed >80% of drug release in 6 mins. This may be due to absence of superdisintegrant in marketed formulation.

Batches F1-F3 were based on Crospovidone XL as superdisintegrant; batches F4-F6 contained Ac-di-sol as superdisintegrant whereas the batches F7-F9 were formulated with sodium starch glycollate.. A direct relationship between the concentration of the superdisintegrant and % *in vitro* dissolution of CINN and DOM were observed. Our results are in agreement with the findings of Devi NK *et al*. [16], Bala *et al*. [17] and Sakr *et al* .[18]

Batches F1-F3; F4-F6 and F7-F9 were subjected to one way ANOVA followed by Tukey-Alpha Multiple Comparisons Test. P value was less than 0.05, which rejects the null hypothesis, thus proving that there is a significant difference between the *in vitro* dissolution profiles obtained.

Optimized batch

Batch F6 with 5% Ac-Di-Sol was chosen as the optimized batch on the basis of shortest disintegration time among all the batches (**Table 5**).

Stability Studies

The formulation F6 was subjected to accelerated stability study and photo stability study. The conditions of the above mentioned studies were 40 ºC /75%RH for three months and 1.2 million lux hours respectively. At the end of the specified time period, the tablets were evaluated for physical appearance, weight variation, thickness, hardness, friability, disintegration time, wetting time, assay, content uniformity and % *in vitro* dissolution (**Table 9**). No significant differences in the values of all the parameters were found when compared to the initial values. The results of stability study indicated that prepared formulation was stable.

Table 1: Formulation of ODTs containing different concentrations of superdisintegrants.

Ingredients	**Batch**								
	F1 (mg)	**F2 (mg)**	**F3 (mg)**	**F4 (mg)**	**F5 (mg)**	**F6 (mg)**	**F7 (mg)**	**F8 (mg)**	**F9 (mg)**
Cinnarizine	20	20	20	20	20	20	20	20	20
Domperidone	15	15	15	15	15	15	15	15	15
Crospovidone XL	**5 (2.5%)**	**10 (5%)**	**15 (7.5%)**	-	-	-	-	-	-
Ac-di-sol SD711		-	-	**2 (1%)**	**6 (3%)**	**10 (5%)**	-	-	-
Sodium Starch Glycollate (Type A)	-	-	-	-	-	-	**8 (4%)**	**12 (6%)**	**16 (8%)**
Microcrystalline cellulose pH102	76.5	74	71.5	78	76	74	75	73	71
Pearlitol 200SD	76.5	74	71.5	78	76	74	75	73	71
Aerosil 200	4	4	4	4	4	4	4	4	4
Aspartame	1	1	1	1	1	1	1	1	1
Sodium Stearyl Fumarate	2	2	2	2	2	2	2	2	2
Total weight (mg)	200	200	200	200	200	200	200	200	200

Table 2: Characterization of API

Properties	**Cinnarizine**	**Domperidone**
Description	Crystalline	Crystalline
Colour	White	White to off white
Odour	Odourless	Odourless
State	Solid	Solid
Assay	98.29±2.12 %	96.53±1.59 %
Bulk density	0.38±0.02gm/ml	0.29±0.01gm/ml
Tapped density	0.5±.01gm/ml	0.38±0.01gm/ml
Angle of repose	47.98 ± 1.2^0	40.36 ± 1.1^0
Carrs index	24±1.1%	23.68±1.2%
Haussners ratio	1.31±0.1	1.32±0.1
Melting Point	120°C	241°C
Saturation solubility	748 mg/L	0.995mg/L

Table 3: Drug-Excipient interaction study

Parameter		**Initial Observation of Lubricated Blend**	**After 1 month**
Physical Observation	Open Petridish	Smooth free flowing powder	Smooth free flowing powder
	Black covered	Smooth free flowing powder	Smooth free flowing powder
	Alu pouch	Smooth free flowing powder	Smooth free flowing powder
DSC		Sharp peak at melting temperature	Sharp peak at melting temperature

Table 4: Pre-compression evaluation parameters.

Property	Values (Mean ± SD) (n=3)								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Angle of repose (˚)	18.2±1.2	22.3±1.3	24.22±1.5	21.8±1.2	20.8±1.6	17.35±1.2	22.19±1.3	21.09±1.2	21.8±1.5
Bulk density (gm/ml)	0.5±0.05	0.5±0.02	0.47±0.03	0.46±0.05	0.42±0.06	0.33±0.05	0.43±0.06	0.44±0.05	0.38±0.02
Tap density (gm/ml)	0.62±0.01	0.62±0.02	0.6±0.08	0.57±0.04	0.55±0.02	0.4±0.05	0.55±0.03	0.53±0.06	0.5±0.05
Carr's index (%)	20±1.30	20±1.8	21.66±1.9	19.29±1.8	24.36±1.9	17.5±1.2	21.09±1.2	16.98±1.25	24±1.5
Hausner's ratio	1.25±0.20	1.25±0.12	1.27±0.32	1.11±0.20	1.32±0.15	1.21±0.20	1.26±0.20	1.21±0.14	1.31±0.06

Table 5: Evaluation parameters of formulated batches.

Batch	**Weight Variation (mg) (n=20)**	**Thickness (mm) (n=10)**	**Hardness (kg/cm^2) (n=10)**	**Friability (%) 25 rpm for 4 mins**	**Disintegration time (sec) (n=6)**	**Wetting time (min) (n=3)**
F1	198-206	4.02±0.01	3.5-4	0.5	12-13	14-17
F2	198-209	4.01±0.01	3-4	0.8	10-11	12-15
F3	196-208	4.02±0.01	3-4	0.7	8-9	8-9
F4	196-207	4.02±0.01	3.5-4	0.25	17-20	23-24
F5	196-204	4.01±0.01	3-4	0.58	14-16	22-26
F6	**196-204**	**4.01±0.01**	**3-4**	**0.50**	**6-7**	**10-11**
F7	198-209	4.01±0.01	3.5-4	0.30	27-28	43-49
F8	198-207	4.02±0.01	3.5-4	0.86	20-23	18-19
F9	200-206	4.01±0.01	3-4	0.48	13-18	15-16
STUGIL	200-205	4.02±0.01	3-4	0.58	7-9mins	8-9mins

Table 6: Evaluation parameters of formulated batches

Batch	**Assay-Lubricated blend CINN (%)**	**Assay-Lubricated blend DOM (%)**	**Assay-Tablets CINN (n=10) (%)**	**Assay-Tablets DOM (n=10) (%)**	**CU-Tablets CINN (n=10) (%)**	**CU -Tablets DOM (n=10) (%)**
F1	103.1±1.2	99.08±1.4	103.1±1.6	106.3±1.1	97.59	99.06-106.3
F2	97.5±1.5	99.06±1.5	103.1±1.6	106.3±1.1	87.5-103.1	99.06-105.3
F3	97.5±1.23	99.06±1.5	97.5±1.3	99.06±1.6	87.5-103.1	99.06-105.3
F4	97.5±1.3	99.06±1.6	97.59±1.5	106.3±1.1	87.5-103.1	95.8-105.3
F5	97.59±1.2	99.08±1.6	103.1±1.5	99.08±1.3	97.5	99.06-105.3
F6	**103.1±1.2**	**105.3±2.5**	**103.1±1.6**	**105.3±1.3**	**87.5-103.1**	**99.06-113.6**
F7	103.1±1.3	106.3±1.5	103.1±1.3	106.3±1.5	87.5-103.1	99.06-113.6
F8	97.59±1.32	99.06±1.4	97.59±1.5	99.06±1.6	87.5-103.1	99.06-106.3
F9	97.59±1.25	99.06±1.5	97.59±1.1	99.06±1.4	87.5-103.1	99.06-106.3
STUGIL	--	--	103.1±1.2	99.06±1.2	97.5-103.1	99.06-106.3

Table 7 *In vitro* dissolution of Cinnarizine

Time (min)	Cumulative % drug release (Mean ± SD)									
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**STUGIL**
2	37.8 ±2.5	54.5 ±2.0	78.75 ±1.9	37.8 ±1.4	50.6 ±2.3	78.75 ±2.5	37.8 ±1.65	50.6 ±1.96	78.75 ±1.48	12.5 ±0.15
4	85.82 ±2.03	87.83 ±1.9	92.81 ±2.5	82.9 ±2.4	88.7 ±2.4	92.8 ±2.45	54.5 ±2.46	78.75 ±2.05	92.81 ±1.65	32.34 ±1.2
6	104.5 ±2.5	106.8 ±2.5	106.8 ±1.6	94.58 ±2.5	104.5 ±1.9	106.8 ±2.56	87.8 ±2.65	92.81 ±1.97	106.8 ±1.78	46.4 ±1.2
8	104.5 ±2.6	106.8 ±2.5	106.8 ±2.5	94.58 ±2.6	104.5 ±2.6	106.8 ±2.4	104.5 ±2.45	106.8 ±2.05	106.8 ±1.96	53.4 ±1.15
10	104.5 ±2.4	106.8 ±2.3	106.8 ±1.5	94.58 ±1.9	104.5 ±2.4	106.8 ±2.45	104.5 ±2.9	106.8 ±2.62	106.8 ±2.06	60.46 ±1.36
15	104.5 ±2.5	106.8 ±2.06	106.8 ±1.6	94.58 ±2.5	104.5 ±2.5	106.8 ±1.96	104.5 ±2.4	106.8 ±1.45	106.8 ±1.79	78.75 ±1.78
20	104.5 ±2.5	106.8 ±2.5	106.8 ±1.9	94.58 ±2.4	104.5 ±1.95	106.8 ±1.65	104.5 ±1.96	106.8 ±1.65	106.8 ±1.48	92.8 ±1.56
30	104.5 ±2.5	106.8 ±2.6	106.8 ±1.4	94.58 ±2.6	104.5 ±2.5	106.8 ±1.45	104.5 ±1.96	106.8 ±1.95	106.8 ±2.05	92.8 ±1.12

Table 8. *In vitro* dissolution of Domperidone

Time (min)	Cumulative % drug release (Mean ± SD)									
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**STUGIL**
2	62.95 ±2.5	65.75 ±1.45	78.95 ±1.78	49.8 ±1.98	56.39 ±2.04	78.75 ±1.45	56.39 ±1.75	69.5 ±2.62	82.2 ±1.45	8.5 ±0.12
4	76.06 ±2.4	82.62 ±2.56	87.83 ±2.69	82.01 ±2.06	85.05 ±2.05	95.73 ±1.96	89.18 ±1.58	95.73 ±2.04	98.9 ±2.65	15.08 ± 0.25
6	82.62 ±2.65	97.92 ±1.78	102.3 ±1.75	95.8 ±2.89	102.2 ±2.68	108.8 ±2.65	95.73 ±2.65	98.9 ±1.96	102.2 ±2.45	21.6 ±1.02
8	85.62 ±2.6	97.92 ±1.96	102.3 ±2.05	95.8 ±1.78	102.2 ±1.58	108.8 ±1.69	102.2 ±1.45	98.9 ±2.08	102.2 ±1.98	28.19 ±1.10
10	85.62 ±1.96	97.92 ±2.5	102.3 ±1.96	95.8 ±2.08	102.2 ±1.49	108.8 ±1.87	102.2 ±1.95	98.9 ±2.56	102.2 ±1.54	34.75 ±1.35
15	85.62 ±2.45	97.92 ±1.45	102.3 ±2.05	95.8 ±1.78	102.2 ±2.58	108.8 ±1.75	102.2 ±2.06	98.9 ±1.48	102.2 ±1.96	95.73 ±2.15
20	85.62 ±1.78	97.92 ±2.69	102.3 ±2.06	95.8 ±1.78	102.2 ±2.65	108.8 ±1.56	102.2 ±2.56	98.9 ±2.36	102.2 ±1.56	95.73 ±2.20
30	85.62 ±1.96	97.92 ±1.58	102.3 ±1.78	95.8 ±2.06	102.2 ±2.05	108.8 ±1.98	102.2 ±2.05	98.9 ±1.56	102.2 ±1.54	95.73 ±1.62

Table 9: Stability studies.

Parameters	**Batch F4**		
	Initial	**After 3 months (Accelerated Stability)**	**After 1.2million lux hours exposure (Photostability)**
Appearance	Round, white tablets	Round, white tablets	Round, white tablets
Weight variation	196-207 mg	195-205 mg	195-205mg
Thickness	4.01±0.02mm	4.01±0.01mm	4.01±0.01mm
Hardness	3-4 kg/cm^2	3-3.5 kg/cm^2	3-3.5kg/cm^2
Friability	0.25%	0.3%	0.3%
D.T.	17-20 sec	16-19 sec	17-19 sec
Wetting time	23-24 sec	22-24 sec	22-25 sec
Assay	103.1±0.15%CINN, 106.3±0.11% DOM	97.59±1.1% CINN 99.08±1.2% DOM	97.59±0.9% CINN, 105.3±1.2% DOM
Content uniformity	87.5-103.1 %CINN,91.8-105.3 %DOM	87.5-103.1 %CINN, 91.8-105.3 %DOM	87.5-103.1 %CINN,91.8-105.3 %DOM
In vitro dissolution (4mins)	94.58±2.5 % CINN, 95.8 ±2.89% DOM	94.58±2.5 % CINN, 95.8 ±2.89% DOM	94.58±2.5 % CINN, 95.8 ±2.89% DOM

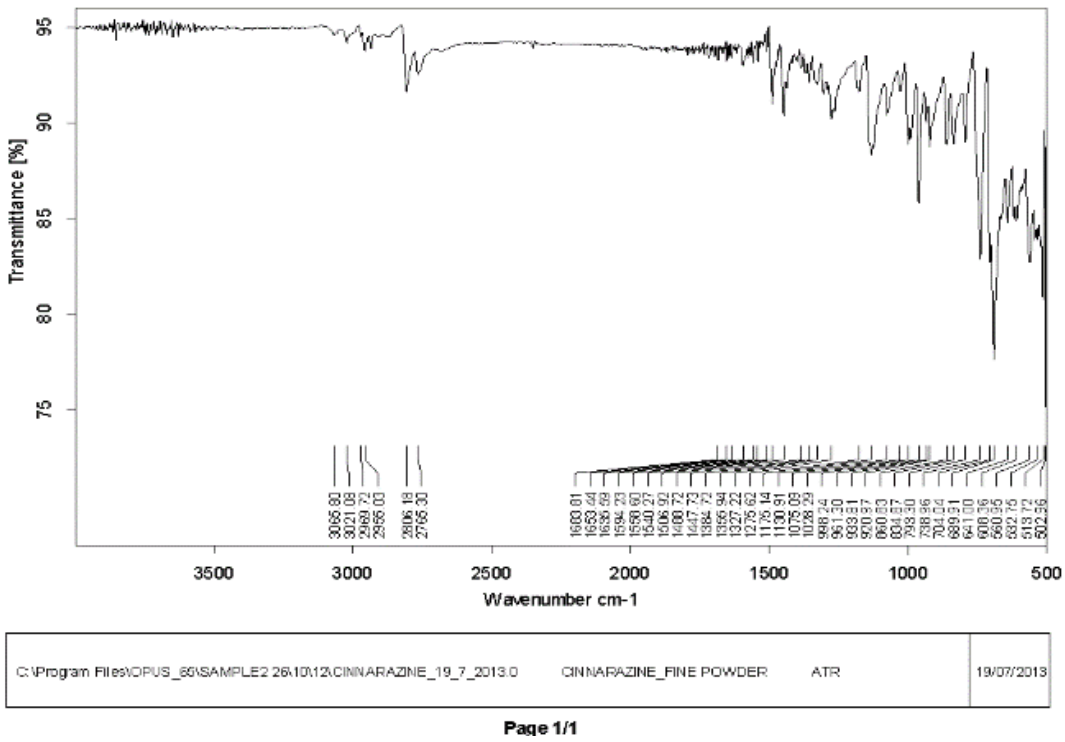

Figure 1: FTIR spectrum of Cinnarizine.

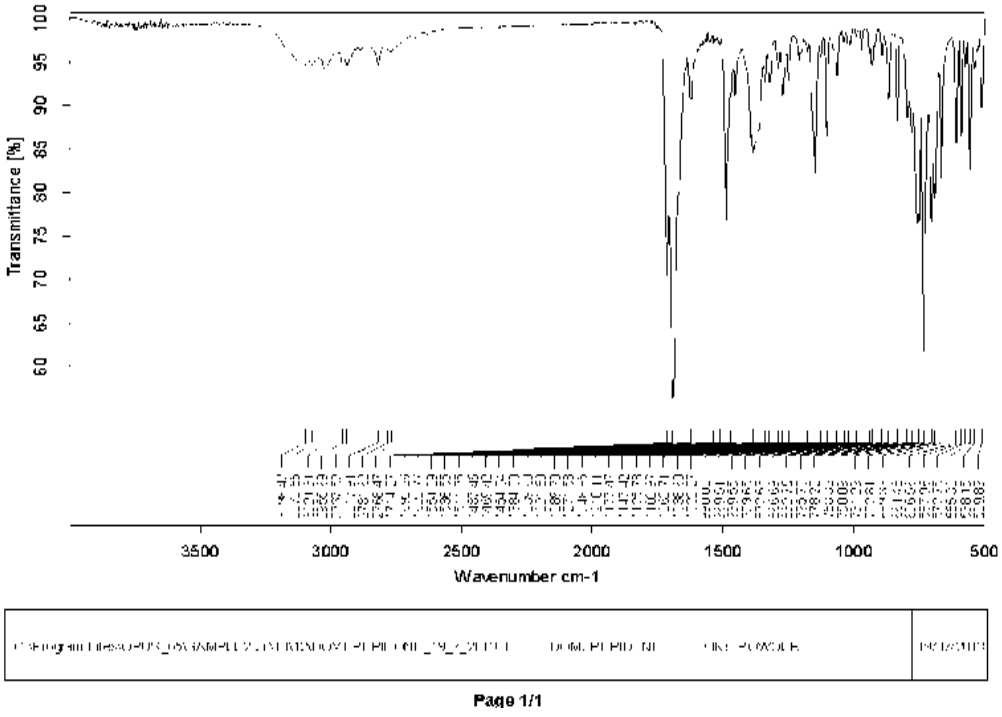

Figure 2: FTIR spectrum of Domperidone.

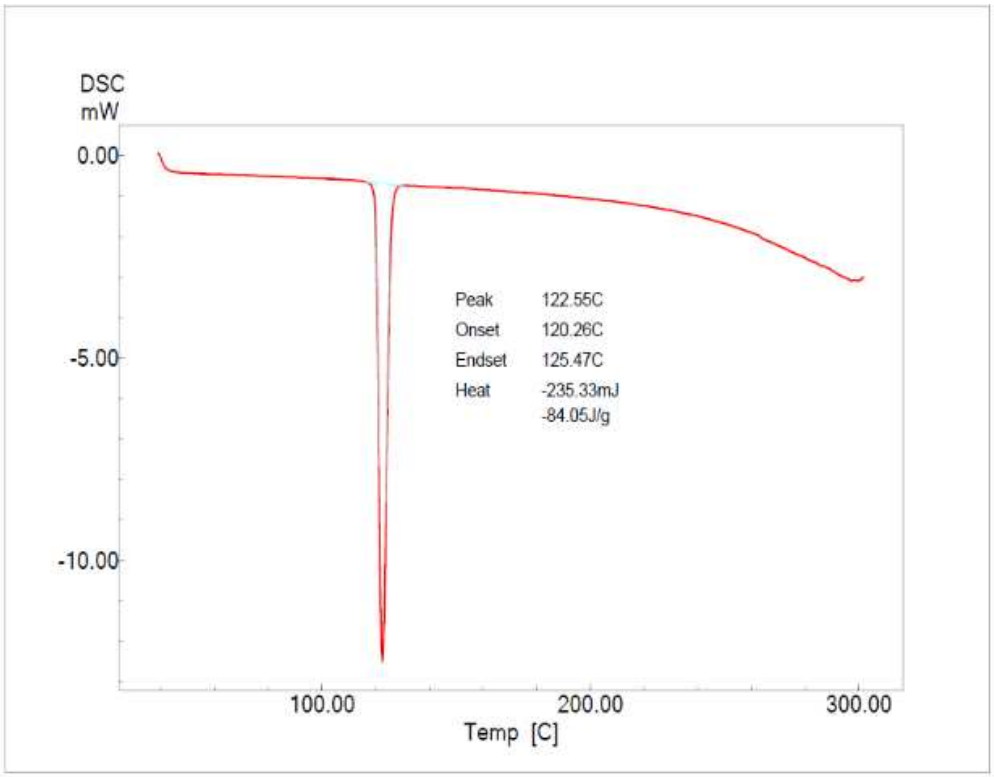

Figure 3: DSC curve of Cinnarizine

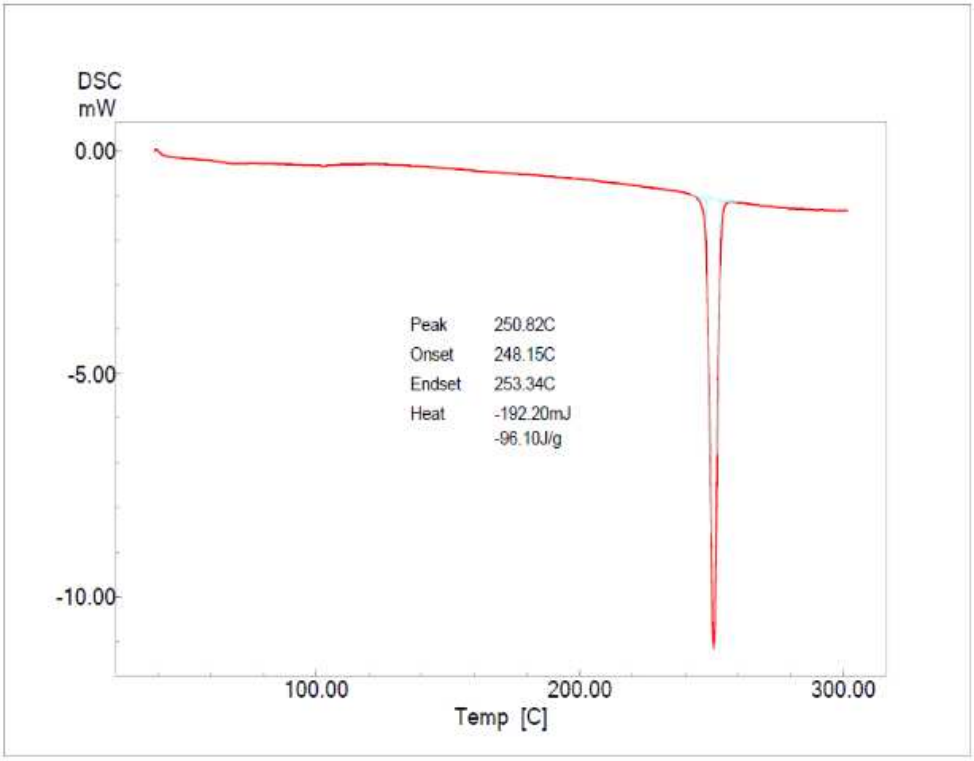

Figure 4: DSC curve of Domperidone

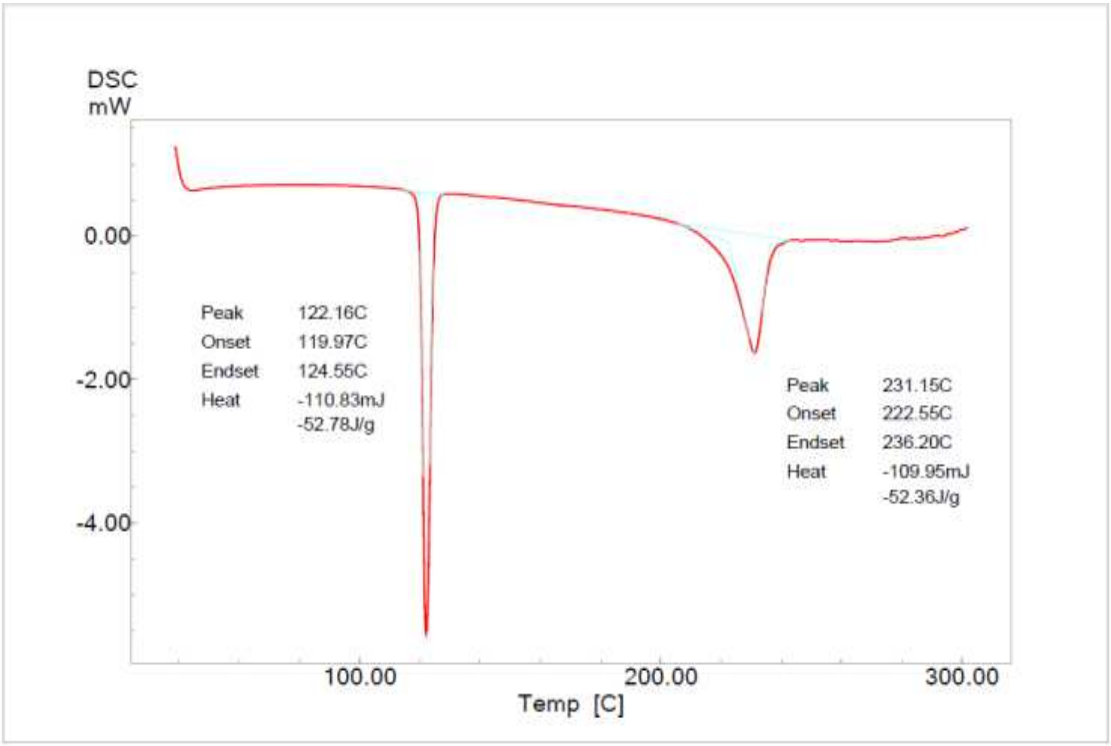

Figure 5: DSC curve of Domperidone and Cinnarizine inphysical mixture

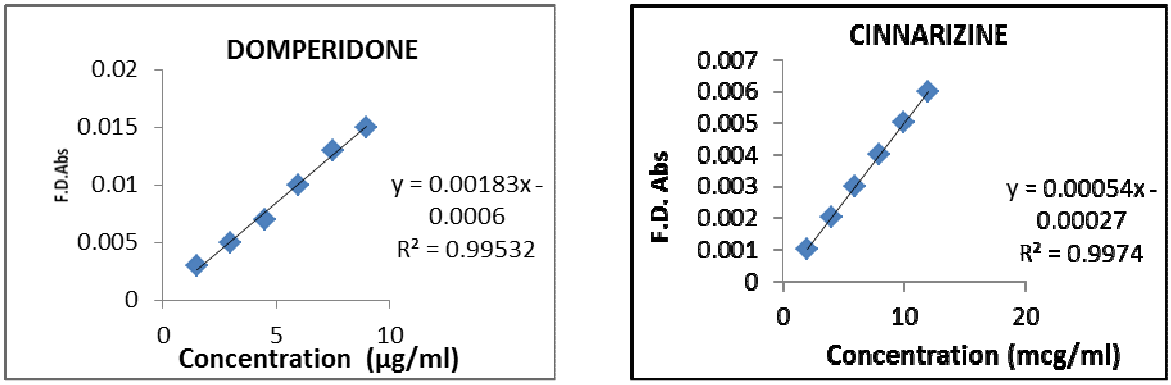

Figure 6: Analytical method development of simultaneous estimation of domperidone and cinnarizine in mixture. (F.D.Abs: First Derivative Absorbance)

4. Conclusion

It was concluded that ODTs of Cinnarizine and Domperidone were successfully prepared by direct compression technique using selected superdisintegrant for the better patient compliance, rapid onset of action and effective therapy.

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6. Declaration of Interest

The authors report no conflicts of interest.

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