

**FORMULATION AND EVALUATION OF CARBIMAZOLE ORODISPERSIBLE TABLET****MOHAMMED IQDAM AL-SHADEEDI<sup>\*</sup>, LAITH H. SAMEIN\*, MUAYAD A. SHEHAB****\*Department of Pharmaceutics, College of Pharmacy, University of Baghdad, Baghdad, Iraq. Email: mishididi@gmail.com****Received: 09 Dec 2012, Revised and Accepted: 23 Jan 2013****ABSTRACT**

**Objective:** The aim of this study was to develop orodispersible tablet of Carbimazole by using simple and cost effective direct compression technique.

**Methods:** By using different types of superdisintegrant (sodium starch glycolate, croscarmellose sodium, crospovidone and Indion 414) at concentrations (2.5, 5 and 7.5 %), mannitol used as diluent. Swelling index was investigated to compare the swelling property of superdisintegrants. The formulations were evaluated for flow properties, wetting time, hardness, friability, content uniformity, in vitro disintegration time, release profile, and compatibility study.

**Results:** the tablet containing Crospovidone at 5% concentration(F2C) showed the least in *vitro* disintegration time (12 sec. $\pm$  1), with excellent flow properties and hardness of (5kg/cm<sup>2</sup>) with acceptable friability ( 0.52%) and weight variation (202 $\pm$ 2.1), and good dissolution profile showed faster dissolution in comparison with conventional dosage form ( D<sub>2min</sub>=75.57 %, 0 ) for F2C and conventional tablet respectively. FTIR and DSC studies were done for the final formula F2C and they showed no drug - excipient incompatibility.

**Conclusion:** It can be concluded that crospovidone gives the best results especially at 5% (w/w) (F2C) for formulation of orodispersible tablets of Carbimazole with better pharmaceutical properties than conventional marketed tablets.

**Keywords:** Carbimazole, Crospovidone, Indion 414, Orodispersible, Direct Compression, Superdisintegrant.

**INTRODUCTION**

The Carbimazole is commonly used orally administered thionamide an antithyroid drug used in the treatment of hyperthyroidism and Grave's disease in Great Britain and Europe[1], Carbimazole a carbethoxy derivative of methimazole, and its antithyroid action is due to its conversion to methimazole after absorption[2].This drug inhibits iodination of tyrosine in thyroglobulin [3]. Many patients that have swallowing problems associated with the marketed dosage form of Carbimazole (carbimazole marketed as solid conventional tablet dosage only) may benefit the orodispersible tablet.

Orodispersible tablets (ODTs) are not only indicated for people who have swallowing difficulties, but also are ideal for active people [4] because orodispersible tablets offer a convenient dosage form that is easy to administer without need of water with improved taste for drugs with bitter taste, all these advantages leads to increased patient compliance and effective therapy. Their growing importance was underlined recently when European pharmacopoeia adopted the term "Orodispersible tablet" as a tablet that to be placed in the mouth where it disperses rapidly before swallowing. According to European pharmacopoeia, the ODT should disperse/disintegrate in less than three minutes. The basic approach in development of ODT is the use of superdisintegrants like crospovidone (crosslinked PVP), croscarmellose (cross linked carboxymethyl cellulose), sodium starch glycolate (cross linked starch ) Indion 414 ( ion exchange resin of polacrilin potassium ), which provide instantaneous disintegration of tablet after putting on tongue, there by release the drug in saliva.

Oro-dispersible tablets (ODTs) are prepared generally by several methods including sublimation, spray drying, and direct compression. Of these approaches, a conventional tablet compression method is used most widely because of its low cost and ease of manufacturing.

So the object of this study was to develop orodispersible tablet of Carbimazole by using" simple and cost effective"[5]direct compression technique.

**MATERIALS AND METHODS****Materials**

Carbimazole(CMZ) powder was obtained as a gift sample from Remedica Pharmaceuticals Ltd, Limassol- Cyprus. Indion 414 was obtained as agift sample from Ion exchange (India), Ltd., sodium

starch glycolate (SSG) Aspartame (ASP), Sodium Starch Glycolate (SSG), and Croscarmellose Sodium (CCS) were supplied by (Samara Drug Industry ( SDI), Iraq. Crospovidone (CP)was supplied by Dar Al Dawa Pharmaceutical Manufacturing Co., Jordan. All other reagents and chemicals used were of analytical grade.

**Methods****Effect of pH on swelling capacity of superdisintegrants**

Swelling capacity or (swelling index ) according to B.P. 2010 is the volume in milliliters occupied by 1 gram of a drug, including any adhering mucilage, after it has swollen in an aqueous liquid for 4hours [6]. One gram of each superdisintegrant was placed in dry cylinder fixed in water bath. Acidic solution (0.1 N HCl) or phosphate buffer (pH 6.8) was added gradually to these dry samples separately with continuous stirring until the volume completed to 100 ml. The samples were incubated at 37°C for 4 hours. The volume of each superdisintegrant was recorded before the addition of the medium and at the end of the incubation time. The test was carried out by using specifications of B.P.

The swelling capacity was calculated using the following equation[7]:

$$\text{Swelling Capacity} = \frac{V_t - V_i}{V_i} \times 100 \quad \dots \quad (1)$$

Where V<sub>i</sub> and V<sub>t</sub> are the initial and final volumes, respectively.

The swelling index is given by the mean of 3 tests.

**Formulation of Orodispersible Tablet****Formulation of Placebo Orodispersible Tablets (without CMZ)**

Different placebo formulas (without CMZ) were prepared and tested to obtain the optimum formula that shows the fastest disintegration time in the mouth ( *in vivo* ) with good flowability and compressibility of powder blend and accepted hardness and friability of prepared tablets. composition of placebo formulae was mentioned in Table 1. All the ingredients were passed through mesh No.60. All formulas were prepared using direct compression technique. Each formula was formulated by mixing ( geometric mixing ) all the ingredients (except the lubricant) for 15 min after which the lubricant was added and blended for another 1minute. The final mixture was compressed using a round beveled edge double punch, Korsch, tablet machine with a 9 mm flat punch. Before

compression, the surface of die and punch were lubricated with magnesium (Mg) stearate[8].The final weight of tablet was adjusted to be 200mg. Different adjustments of the machine settings were tried. The adjustment giving the highest possible hardness value with the highest accepted disintegration time was selected and applied to all tablet formulations[9].

#### Formulation of Carbimazole Orodispersible Tablets

F7and F8 were selected to be Carbimazole loaded formulae because of their fastest disintegration time (F8) (promising formula F2C) and

to study the effect of CP concentration on the dissolution rate of the drug (F1C formula). Carbimazole 5 mg for each tablet was added, the amount of the diluent (Mannitol) was decreased by 5 mg for each tablet of the formula, the total weight of each tablet was maintained at 200 mg as shown in Table 2. the drug was passed through mesh No.60. mixing ( geometric mixing ) all the ingredients and Carbimazole (except the lubricant) for 15 min after which the lubricant was added and blended for another 1minute. The final mixture was compressed using a double punch, Korsch, tablet machine with a 9 mm flat punch.as per for placebo formulae

**Table 1: Composition of the placebo Orodispersible Formulae**

Material(mg)	Formula Code												
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13
SSG	5	10	15										5
CCS				5	10	15							5
CP							5	10	15				
INDION 414										5	10	15	
Mannitol	187	182	177	187	182	177	187	182	177	187	182	177	182
ASP	2	2	2	2	2	2	2	2	2	2	2	2	2
Talc	4	4	4	4	4	4	4	4	4	4	4	4	4
Mg stearate	2	2	2	2	2	2	2	2	2	2	2	2	2
Total weight(mg)	200	200	200	200	200	200	200	200	200	200	200	200	200

**Table 2: Composition of the Selected Carbimazole Orodispersible Tablet Formulae**

Material (mg)	Formula Code	
	F1C	F2C
Carbimazole	5	5
crospovidone	5	10
aspartame	2	2
Talc	4	4
Mg stearate	2	2
Mannitol Q.S. to	200	200

#### Evaluation of Powder Flowability

##### Angle of Repose

Angle of repose(  $\theta$  ) was determined using funnel method. The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. The radius of the heap (r) was measured and angle of repose was calculated using the following equation [10]:

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

##### Compressibility, Carr's consolidation index:

A sample of each formula of the prepared orodispersible powder was poured into a volumetric cylinder to occupy an initial volume ( $V_0$ ) and then the cylinder was subjected to a standard tapping procedure by Electrical densometer 1000 times tapping or until a constant volume was achieved ( $V_p$ ).

The compressibility index then calculated using the following equation [11]:

$$\text{Compressibility Index (\%)} = \frac{V_0 - V_p}{V_0} \times 100 \quad (3)$$

#### Evaluation of orodispersible tablets

##### Weight variation test

Weight variation test was done by weighing 20 (randomly selected) tablets individually. To pass this test, none of the tablets of each formula deviated from the average weight by more or less than 7.5%[12].

##### Hardness

The crushing strength of the tablets was measured using a manual Monsanto hardness tester. Three tablets from each formula batch

were tested randomly and the average reading $\pm$  SD was recorded[13].

##### Friability

Twenty tablet were weighed and placed in a Roche friabilator and the equipment was recorded at 25 rpm for 4min. The tablets were taken out, de dusted, and reweighed. The percentage friability of the tablets was calculated using the following equation [14]

$$\% \text{ friability} = \frac{\text{Initial weight} - \text{final weight}}{\text{Initial weight}} \times 100 \quad (4)$$

##### In Vivo Disintegration Time Test

In vivo Disintegration Time is the time required for the tablets to disperse in mouth cavity. The test was performed in 3 healthy human volunteers in the age group of 23 to 28 years for all the placebo prepared orodispersible tablets (without CMZ). Prior to the test, all volunteers got a detailed briefing on purpose of this test, then they were asked to rinse their mouth with water. Then the prepared orodispersible tablet was placed on the tongue and immediately a stopwatch was started. They were allowed to move the orodispersible tablet against the upper palate of the mouth with their tongue to cause a gentle tumbling action on the tablet without chewing or moving it from side to side. Immediately after the last noticeable granule or fragment had disappeared, the stopwatch was stopped and the time was recorded. Saliva was rinsed from the mouth after each measurement. To check reproducibility, each volunteer repeated the test three times [15].

##### In vitro Disintegration time

In vitro the disintegration time was determined using conventional disintegration test apparatus, a tablet was placed into 200 ml distilled water tube at  $37 \pm 2^\circ\text{C}$  in the disintegration test apparatus. The disintegration time was defined as the time required for the

ODT to completely disintegrate until no solid residue remains on the screen. A stopwatch was used to measure the disintegration time to the nearest second. Only one ODT was analyzed at a time in order to ensure maximum accuracy, the test was done for 3 tablets of each formula [16].

#### Wetting time

Wetting time is closely related to the inner structure of tablets and to the inner structure of tablets and to hydrophilicity of excipients. It is obvious that pore size become smaller (decrease in porosity) and A piece of tissue paper folded twice was kept in a small Petri dish (inter diameter 5.5cm) containing 6 ml of simulated saliva (pH 6.8). Eosin, a water soluble dye, is added to culture dish[17].The tablet was placed on the tissue paper and allowed to wet completely. The time required for complete wetting of the tablet was then recorded[18].

#### Content uniformity

Twenty tablets was taken for each formula that loaded with Carbimazole F1C and F2C. single tablet was powdered and dissolved in 500 mL of distilled water and the absorbance of the final solution was measured at the maximum at 291 nm to determine content of Carbimazole. This test is used to determine whether the individual contents are within limits set with reference to the average content of the sample. The preparation complies with the test if each individual content is 85 to 115 per cent of the average content [19].

#### In vitro Dissolution study

In vitro dissolution studies of tablets were performed using the USP Method II ( paddle ) speed at 50 rpm, and 900 ml 0.1N HCl was used as dissolution media maintained at  $37 \pm 0.5^\circ\text{C}$ . Five milliliters of samples were withdrawn at specified time intervals. The volume of dissolution fluid was adjusted to 900 ml, by replacing each 5 ml aliquot withdrawn with 5 ml of 0.1N HCl, pre-warmed at  $37 \pm 0.5^\circ\text{C}$ . Samples withdrawn were filtered through Whatmann filter paper, and analyzed at 291 nm. In addition, the release profiles of the NEOMERCAZOLE® Tablets were also determined at the same test environments.. Then the cumulative percentage of drug release was calculated and represent graphically[20].

#### Compatibility Studies

##### Fourier transform infrared spectroscopy (FTIR)

Drug-excipient interaction is one of the most important compatibility studies, and Fourier Transform InfraredSpectroscopy (FTIR) study was used for this purpose on samples of pure Carbimazole (CMZ), crospovidone (CP), mannitol, physical mixture of ( 1:1:1) CMZ, CP, and mannitol respectively, Blend powder of F2C formula, and F2C tablet.Spectra were obtained using( Shimadzu 8300, Japan)according to KBR disk method. About 2-3 mg of samples were mixed with dried IR grade potassium bromide powder and the spectra were in between the wave number range of 4000-400cm<sup>-1</sup>[21].

##### Differential Scanning Calorimeter (DSC) Study

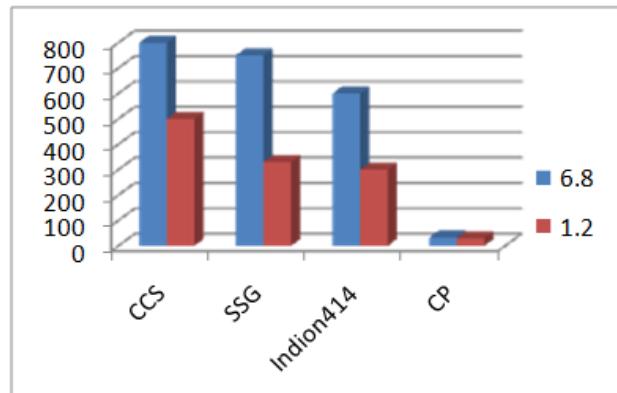
DSC thermogram of pure drug , F2Cpowder blend and F2C compressed tablet were performed by approximately 5 mg of the sample was scanned by using automatic thermal analyzer(DSC60 Shimadzu Corporation, japan)[18].

#### RESULTS AND DISCUSSION

##### Effect of pH on swelling capacity of superdisintegrants

The swelling capacities of the superdisintegrants ( CP, CCS, SSG, and Indion 414) were shown in Fig. 1.The results showed that swelling capacity of CCS and SSG and indion 4104 was higher in pH 6.8 (800 %, 750 % and 600 % respectively) than in pH 1.2 (560%, 330%and 300% respectively). In contrast, CP maintained the same swelling capacity value in both pHs (about 30%). The reason behind the reduction of the swelling capacity of CCS, SSG and Indion 414 in acidic environment can be understood by knowing that all of them are ionic molecules (contain ionizable carboxyl group in their structures). In basic media, the carboxyl group becomes ionized

(anion) and thus, more chance for water attraction and water uptake can take place. Besides the negative charges that develop on the surface of the molecules increase the repulsion force between them and by doing so; more swelling will be achieved. This mechanism is quite opposite in acidic medium. In comparison, CP are non-ionic neutral molecules and that's why it retains its swelling capacity in acidic environment.



**Fig. 1: Swelling capacity of different superdisintegrants sodium starch glycolate(SSG), croscarmellose sodium ( CCS), Indion414 and crospovidone (CP)in 0.1 N HCl (pH 1.2) and phosphate buffer (pH 6.5) at  $37 \pm 0.5^\circ\text{C}$**

##### Evaluation of powder flowability

###### Angle of repose:

Angle of repose ( Table 3) of all formulation batches from F1 to F13, F1C and F2C was found in the range of 20 to  $30^\circ$  which indicates excellent to good flow character.

###### Compressibility Carr's consolidation index

Compressibility (Carr's) index( Table 3) was calculated for all formulation batches and was found to be from 13 to 22.9 which indicates excellent to passable flow [22].

##### Evaluation of orodispersible tablets

###### Weight variation

Due to the better flow properties of all formulation batches, all tablets obtained were of uniform weight with acceptable variation, as shown in Table 4.

###### Hardness

Hardness of all formulation batches were found in the range of 3.0 to 5.0 Kg/cm<sup>2</sup>.

###### Friability

Friability of all formulation batches were found between 0.52 to 0.94 %(Except for formulae F1and F2) which indicating good mechanical resistance of tablets except for tablet with SSG as superdisintegrant due to its effect of weakening the bonds that hold the tablet matrix together.

###### Content uniformity

Drug content of F1C and F2C was found between 99.08 to 101.06%.

##### Wetting time

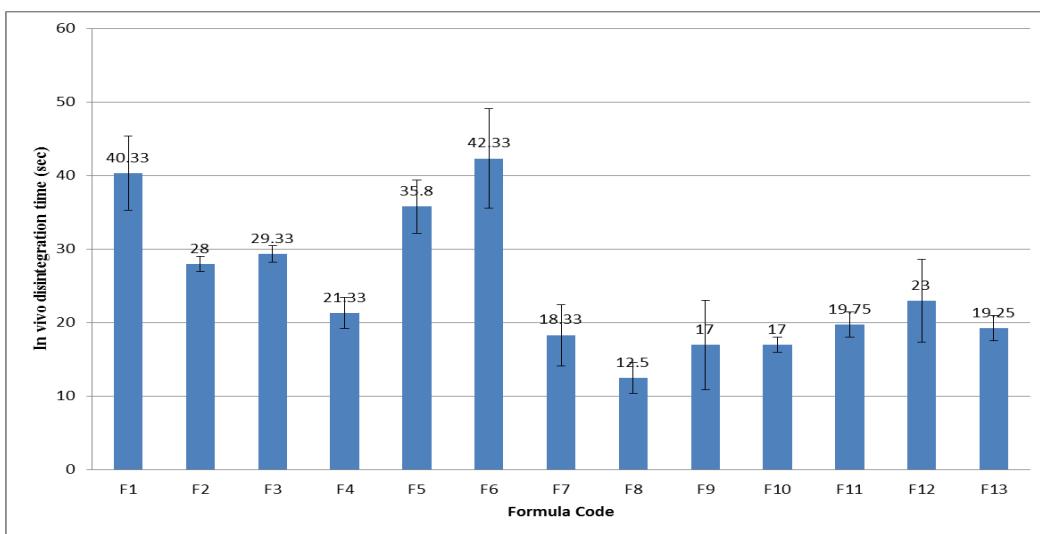
Wetting time of all formulation batches were found in the range of 6 to 74 seconds which predicts a wide range of wetting time due to the major effect of superdisintegrant type due to different mechanisms of disintegration for the superdisintegrant like swelling and wicking superdisintegrants that shows swelling behavior showed a prolonged wetting time at high concentrations and showed an increase of wetting time with concentration due to gel forming property ( except indion 414 which shows no gel forming behavior but it is effective in 2.5%), F8 which contain 5%CP showed the least wetting time.

**Table 3: Flow properties of the prepared formulae**

Property	Formula Code														
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F1C	F2C
Angle of repose	26 <sup>±0.7</sup>	21±1 <sup>.7</sup>	24±2 <sup>.4</sup>	22±0 <sup>.9</sup>	21±5 <sup>.2</sup>	23±3 <sup>.3</sup>	25 <sup>±6.4</sup>	23.5±2 <sup>2</sup>	30±0. <sup>3</sup>	28±4. <sup>3</sup>	22±0. <sup>3</sup>	26.6±0. <sup>0</sup>	20±1. <sup>3</sup>	24±2 <sup>.2</sup>	22.5±0.1
Carr's index	20.7 <sup>±0.8</sup>	22.6 <sup>±2</sup>	23±0 <sup>.8</sup>	20±0 <sup>.9</sup>	18±1 <sup>.3</sup>	18±1 <sup>.1</sup>	14±0. <sup>2</sup>	13.3±0.1 <sup>0.1</sup>	19.4±0. <sup>1.7</sup>	15.4±0. <sup>1.1</sup>	22.9±0. <sup>0.8</sup>	22.7±0. <sup>0.8</sup>	16.8±0. <sup>0.9</sup>	13±0 <sup>.8</sup>	13±0.5

**Table 4: Physical Properties of Placebo Orosoluble Tablets**

Formula No.	Property				
	In vitro DT (sec)	Wetting time(sec)	Hardness (kg/cm <sup>2</sup> )	Friability %	Weight variation (mg)
F1	35.67±0.58	61.67±4.93	3.33±0.28	>1	202.4±2.4
F2	23.33±0.58	33.67±6.03	3.87±0.25	>1	201.56±3.3
F3	20.67±0.58	25±1	3.5±0.5	0.94	203.28±3.1
F4	19±1	35±5	3.67±0.58	0.92	203.6±3.5
F5	27±1	63±2	4±0.5	0.89	202.1±4.0
F6	36.33±1.5	74 ±1	4.5±0.5	0.9	203.7±4.7
F7	23±3.6	15±1	4±0.0	0.73	203.2±3.7
F8	12±2.1	6±0.0	5±0.0	0.62	197.3±2.3
F9	19±1	9.5±0.5	3.67±0.29	0.73	203.2±4.4
F10	12±0	14±1	5±0.0	0.9	199.5±2, 6
F11	26.5±2.5	29±1	4±0.0	0.82	199.1±1.8
F12	31.33±1.52	30±4.24	4.0±0.0	0.75	200.5±1.9
F13	17.67±1.15	24.5±0.5	3±0.0	0.89	199.7±2
F1C	16±1	14±1	3±0.0	0.81	201.0±3.3
F2C	12±1	8±0.33	5.0±0.5	0.52	202±2.1

**Fig. 2: In vivo disintegration time (sec) of F1-F13 as(n=3) mean ± SD**

#### **In Vivo Disintegration time**

In vivo disintegration time as shown in figure.2 were in the range of 12.5-42.33 sec. and CP 5% in F8 shows the least in vivo time 12.5 sec., in vivo study indicate that the effective concentration of CCS and indion 414 was 2.5% but for SSG is 7.5 %.

#### **In vitro Disintegration time**

In vitro disintegration time results as shown in table.4 were the same pattern of the in vivo test but the differences emerged from the difference in fluid volume used (200mL) in comparison to the saliva volume in vivo and the mechanical effect of the tongue in vivo that is not simulated in vitro test[23].

#### **In vitro Dissolution study**

Dissolution studies were done and dissolution parameters D2min and t<sub>80%</sub> are considered for comparison, results showed that there is no significant difference between the dissolution of the 2.5% and 5%

CP containing tablet (F1C and F2C respectively) because of their fast disintegration time < 20 sec. with D2min and t<sub>80%</sub> of 75.57% and 2.3 min respectively. The prepared orosoluble tablet showed fastest release in comparison with marketed NEOMERCAZOLE® Tablets that showed D2min and t<sub>80%</sub> of 0 and 13.6 min respectively (Figure.3).

#### **Compatibility Studies**

##### **Fourier transforms infrared spectroscopy (FTIR)**

FTIR spectra of Mannitol, crospovidone(CP), Carbimazole (CMZ), 1:1:1 ratio of CMZ, CP and Mannitol blend, Blend powder of F2C formula, and F2C tablet are given in Figures ( 4 - 9 ). The results of the FTIR analysis showed that the peaks and the pattern of the spectra were similar in all cases, which indicates that there was no chemical interaction or decomposition of Carbimazole during the process of preparation and handling of the orosoluble tablets[24].

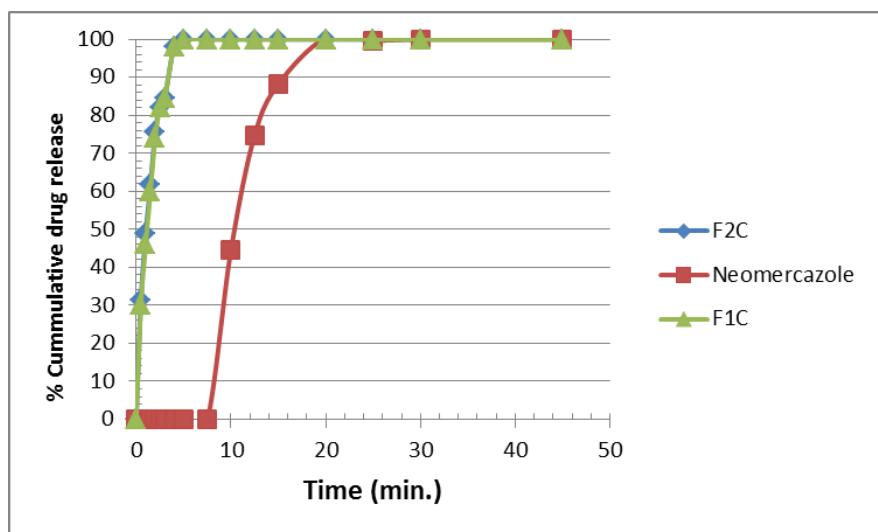


Fig. 3: Dissolution of F1C, F2C, and NEOMERCAZOLE®tablets in 900 mL pH 1.2

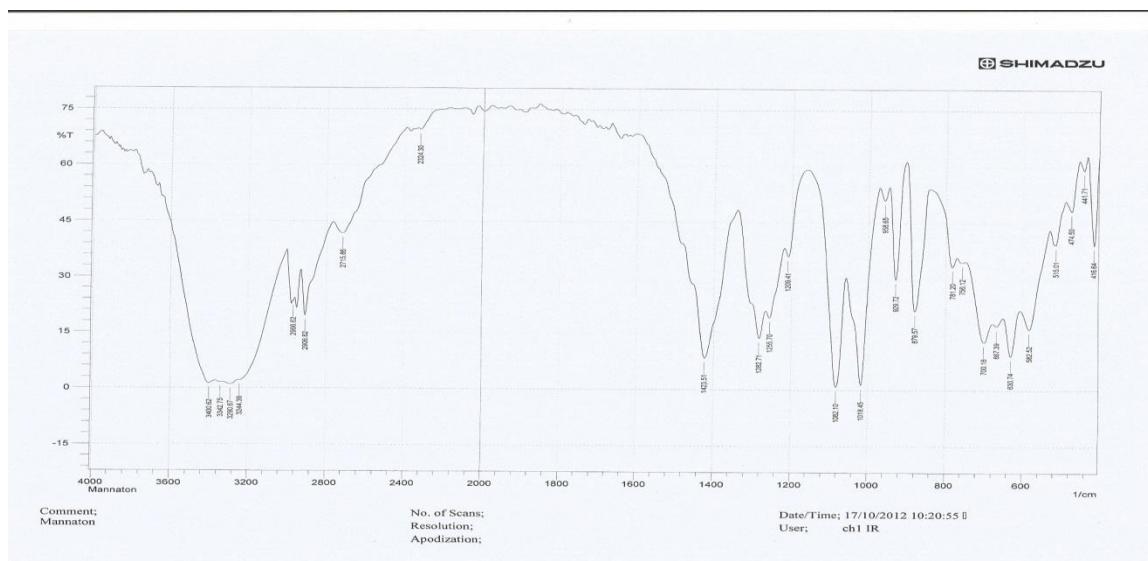


Fig. 4: FTIR Spectrum of pure mannitol

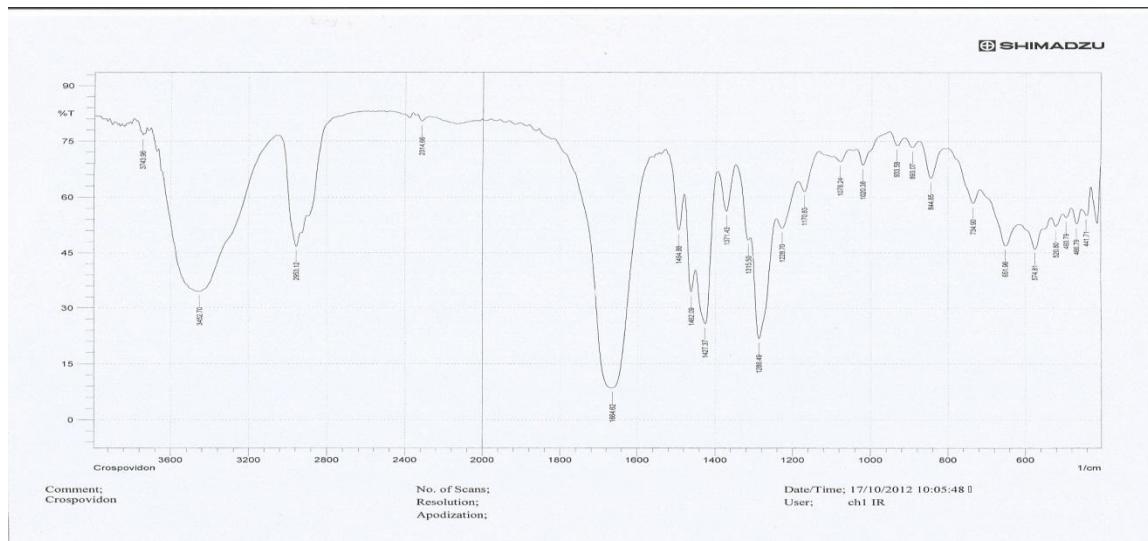


Fig. 5: FTIR spectrum of crospovidone

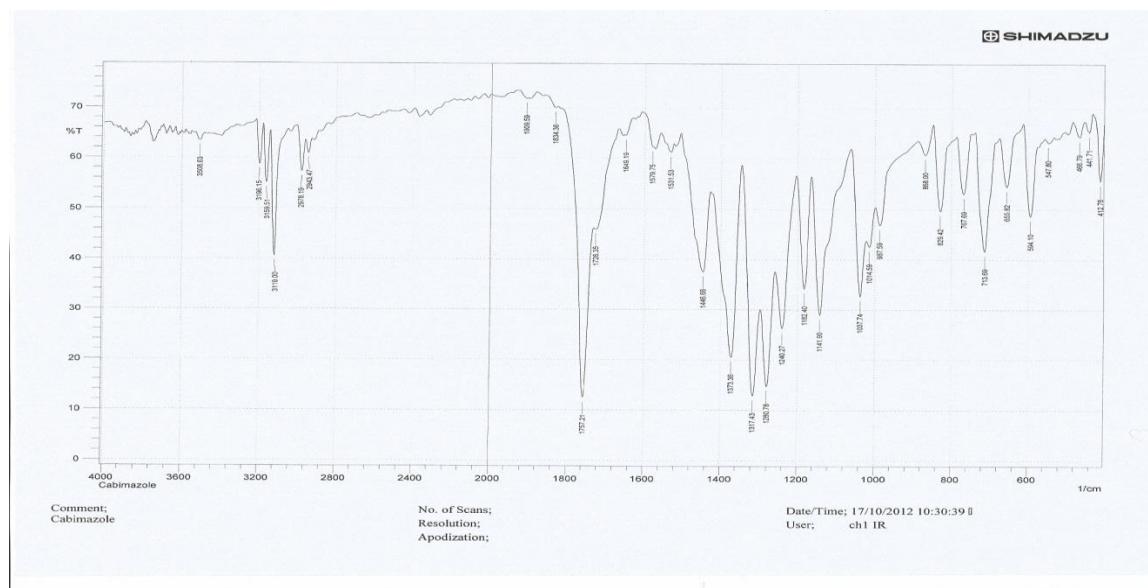


Fig. 6: FTIR Spectrum of pure Carbimazole

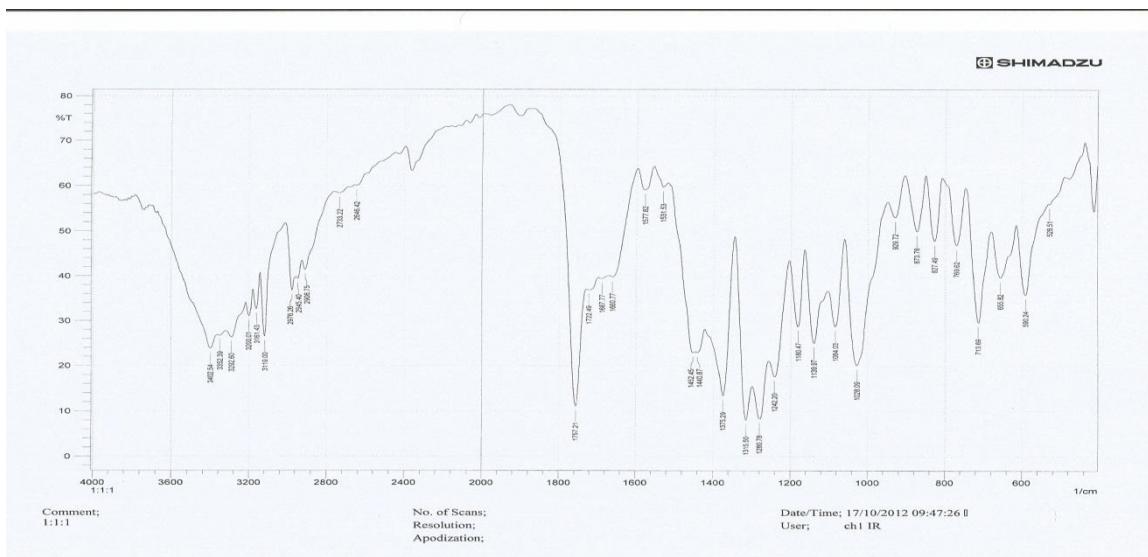


Fig. 7: FTIR spectrum of 1:1:1 Carbimazole, crospovidone, and mannitol

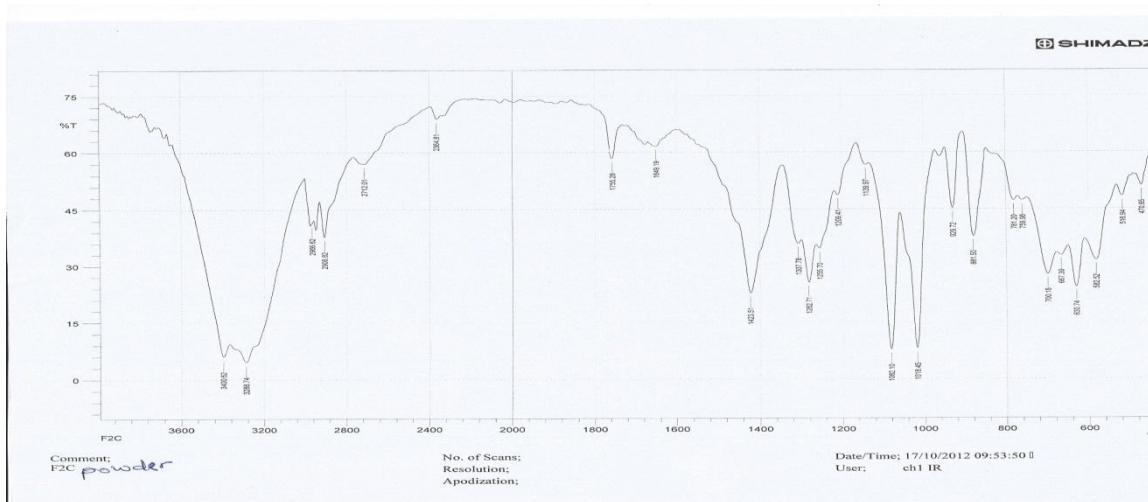


Fig. 8: FTIR spectrum of F2C powder blend

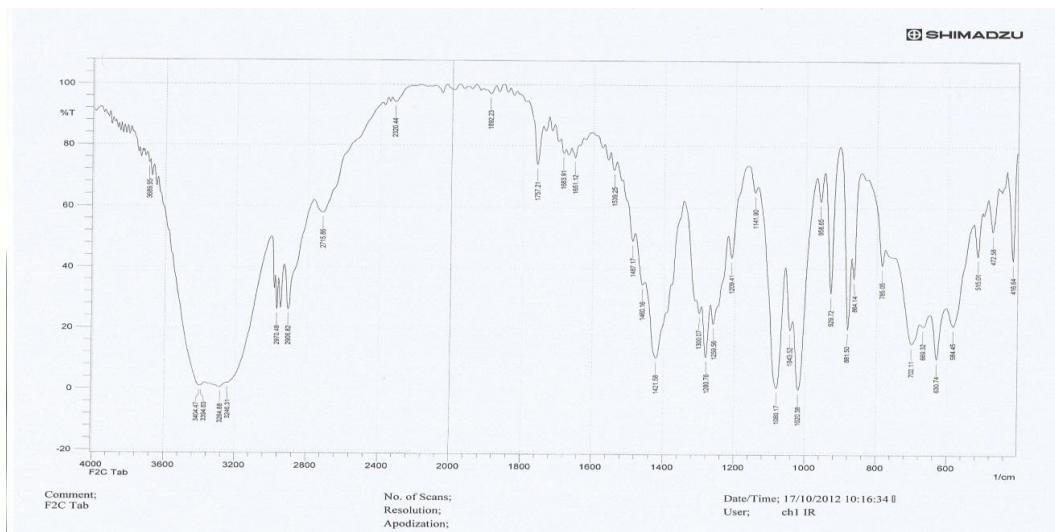


Fig. 9: FTIR spectrum of F2C tablet

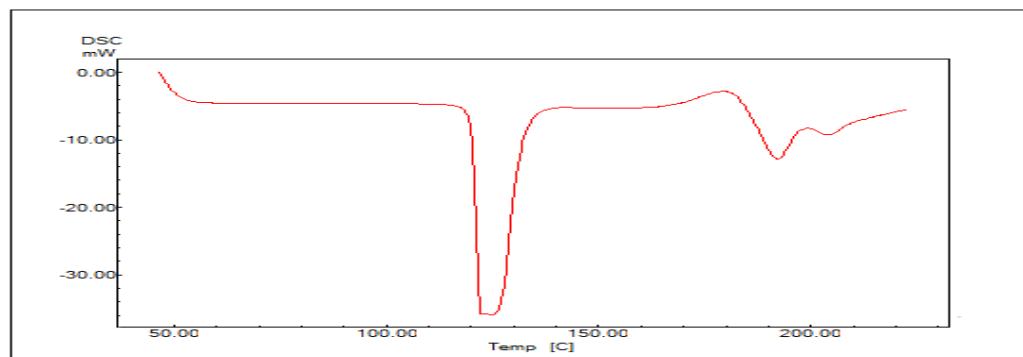


Fig. 10: DSC thermogram of pure carbimazole

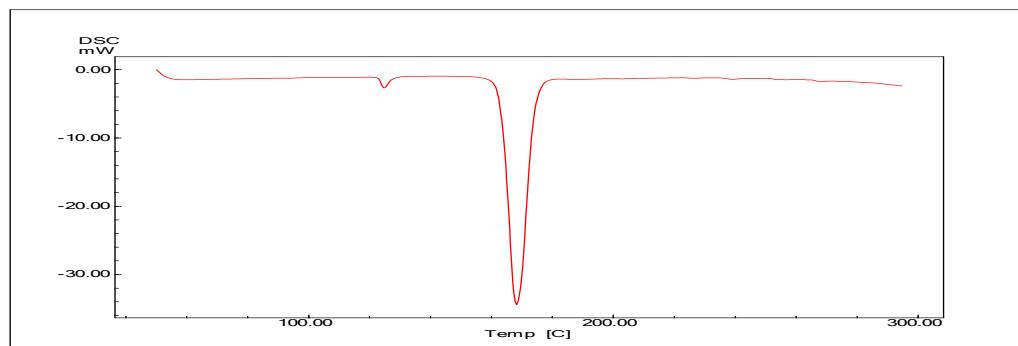


Fig. 11: DSC thermogram of F2C powder blend

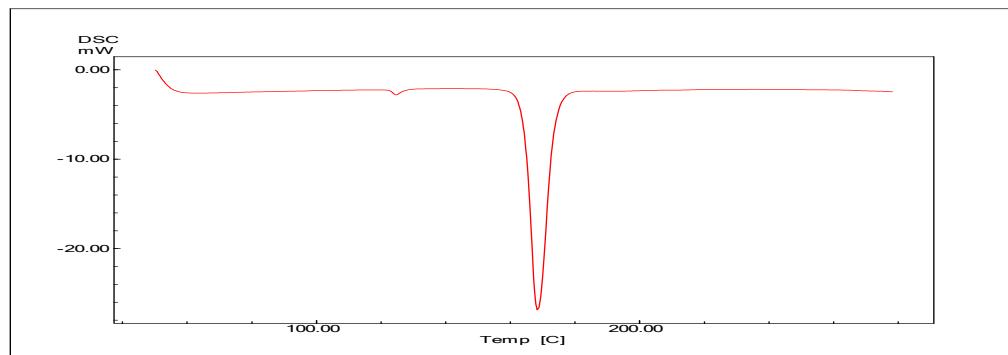


Fig. 12: DSC thermogram of F2C tablet

### Differential Scanning Calorimeter (DSC) Study

Thermograms of Carbimazole pure drug, physical mixture of F2C, and F2C compressed tablet are given in Figures ( 10-12 ). Figure.10 shows a major peak at 223.5 °C which represent melting point of Carbimazole as reported by BP [6], Figure.11 showed a peak of melting of mannitol[6] in range of 166-169°C, Figures ( 11-12 ) were both showing the peak of mannitol and Carbimazole with no change in their positions which indicates no drug-excipients interaction occurred.

### CONCLUSION

Overall, the results suggest that convenience of formulation of orodispersible tablets of Carbimazole containing 5% CP (polyplasdone XL) as a super disintegrant. The optimum selected formula(F2C) has satisfactory physical resistance, fast *in vitro*disintegration time, faster dissolution rate, and no incompatibility problems.

### ACKNOWLEDGMENT

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