

**TASTE MASKING OF DICYCLOMINE HYDROCHLORIDE BY POLYMER CARRIER SYSTEM AND FORMULATION OF ORAL DISINTEGRATING TABLETS**

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Email: drsvk.sscp@gmail.com**ABSTRACT**

Dicyclomine hydrochloride is anticholinergic drug used as an antispasmodic. It is very bitter in taste. The purpose of this research was to develop a bitterless oral disintegrating tablet of Dicyclomine hydrochloride. Taste masking was done by complexing Dicyclomine hydrochloride with Eudragit E-100. Drug polymer complexes were prepared in the ratio 1:1, 1:2 and 1:3 by solvent evaporation method and 1:3 ratio was selected which shows least drug release in SSF ( $4.9 \pm 0.31\%$ ). Three superdisintegrants were used while preparing the tablets e.g. croscarmellose sodium, sodium starch glycolate and crospovidone. The tablets were evaluated for different parameters like thickness, weight variation, hardness, friability, disintegration time, *in vitro* dispersion time, wetting time and drug content uniformity for tablets was found to be within the official limits. Tablets that were formulated by direct compression method using Crospovidone (6%) i.e. optimized formulation F9 exhibited quicker disintegration of tablets than compared to those of Croscarmellose sodium and Sodium starch glycolate. The stability studies were carried out according to ICH guideline which indicates that the selected formulations were stable.

**Keywords:** Dicyclomine hydrochloride, Eudragit E-100, Oral disintegrating tablets, Super disintegrating agents, Taste masking.

**INTRODUCTION**

In recent decades, a variety of pharmaceutical research has been conducted to develop new dosage forms. Considering quality of life, most of these efforts have been focused on ease of medication. Among the various dosage forms developed to improve the ease of administration, the oral disintegrating tablet (ODT) is the most widely preferred commercial products.<sup>1,2</sup>

The ODT has remarkable disintegration properties; it can rapidly disintegrate without water in the mouth within a few seconds. When an ODT is placed in the oral cavity, saliva quickly penetrates into the pores causing rapid disintegration.<sup>3</sup> The ODT presents considerable advantages for the patient (or elder) who cannot swallow (Dysphagia), or who is not permitted water intake because of disease. Such tablets can be produced by various methods; Namely, 1) drying after filling the pockets of the press through pack (PTP) with dispersed solution of the drug, 2) drying after low-pressure compression of humid powder granules containing the drug, 3) compression of dry powder granules containing the drug and, shaping by direct compression after mixing excipients and the drug.<sup>4</sup>

Dicyclomine hydrochloride is tertiary amine used as an antispasmodic. It exerts some nonspecific direct relaxant effect on smooth muscle. In therapeutic doses they decrease spasm of the gastrointestinal tract, biliary tract, ureter and uterus.<sup>5</sup>

Dicyclomine hydrochloride is very bitter in taste, therefore in present study efforts were made to mask the taste of dicyclomine hydrochloride and to formulate fast disintegrating tablets with good mouth feel so as to prepare a "patient-friendly" dosage form.

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

Dicyclomine hydrochloride was a gift from Indoco Remedies Ltd, (Navi Mumbai, India). Eudragit E-100 was a gift from Strides arcolab, (Bangalore, India). Croscarmellose sodium, sodium starch glycolate, crospovidone, avicel PH 101, mannitol, aspartame, vanilla, aerosil and magnesium stearate were obtained from commercial sources.

**Compatibility studies**

The drug-polymer compatibility studies were carried out using Fourier Transform Infrared Spectrophotometer (FTIR). Infra red

spectra of pure drug and mixture of drug and polymer were recorded. A base line correction was made using dried potassium bromide and then the spectra of the dried mixture of drug, formulation mixture and potassium bromide were recorded on FTIR.

**Preparation of taste masked granules of dicyclomine hydrochloride by solvent evaporation method.**

Dicyclomine hydrochloride was thoroughly mixed with powdered Eudragit E-100 in different ratios. Then chloroform was added to this mixture in a glass beaker until the mixture was completely dissolved and to get clear solution. The solution was poured in to the petri plate. Chloroform was removed by solvent evaporation overnight at room temperature. Subsequently the solidified drug polymer complex (DPC) was scraped from the petri plate and grind to get taste masked granules.

Three batches were prepared containing drug-eudragit E-100 in the ratio of 1:1, 1:2, and 1:3 in chloroform by the above-mentioned method.<sup>6</sup>

**Characterization of DPC*****In vitro* taste evaluation**

*In vitro* taste was evaluated by determining drug release in simulated salivary fluid (SSF) (pH 6.8) to predict release in the human saliva. DPC, equivalent to 20 mg of Dicyclomine hydrochloride (i.e., its dose), was placed in 10 ml of SSF and shaken for 60 seconds and make up to the volume 100 ml with SSF. The amount of drug released was analyzed at 215 nm.

On the basis of observations shown in table No. 1 Drug polymer ratio 1:3 was finalized for further study.<sup>7</sup>

**Table 1: *In vitro* taste evaluation of DPCs in SSF**

Sl. No	Drug-Polymer Ratio in DPC	% Drug Dissolved in SSF*
1	1:1	48 ± 0.24
2	1:2	21 ± 0.11
3	1:3	4.9 ± 0.31

\*Results are the mean of 3 observations ± SD.

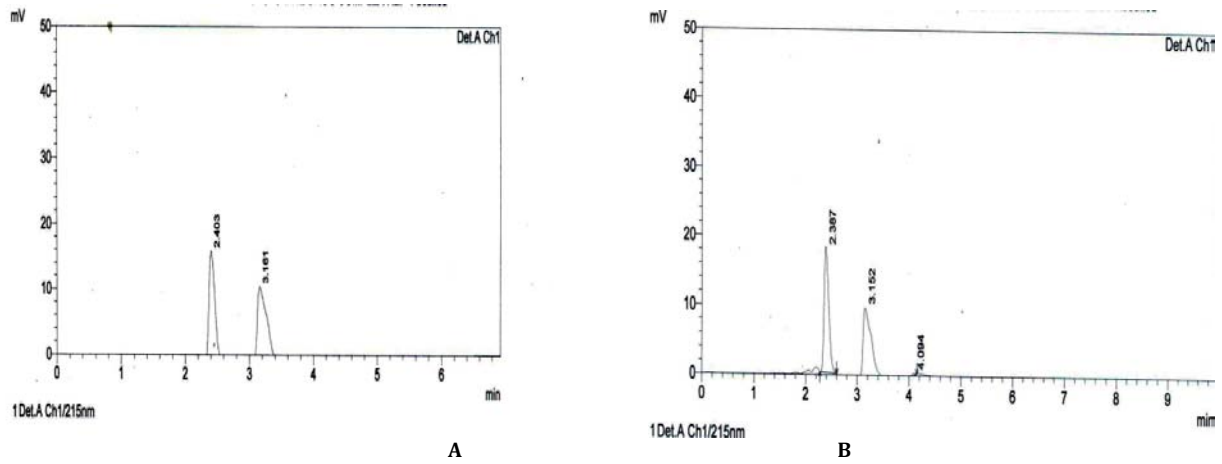


Fig. 1: Chromatogram of pure drug (A) and DPC 1:3 (B)

Table 2: Estimation of drug content in DPC 1:3

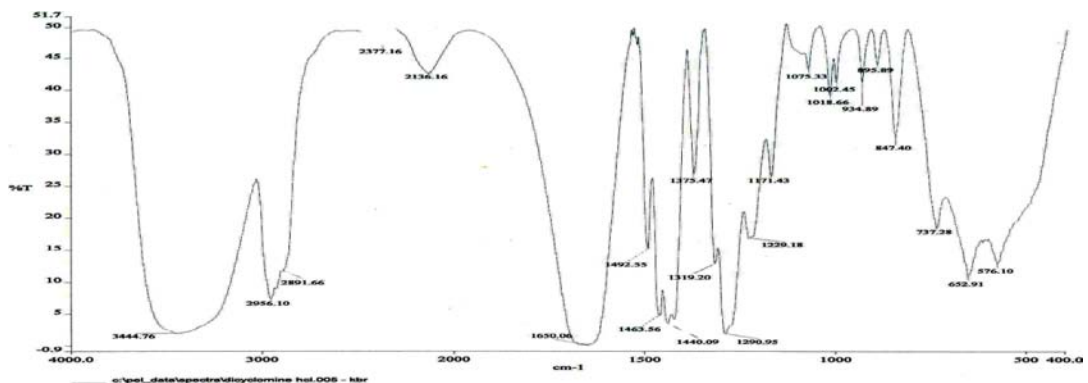
Peak #	Ret. Time (min)	Area	% Of drug content	Drug present (mg)
A1	2.403	119948	100	20
B1	2.387	115002	95.87	19.17

Table 3: Amount drug present in DPC 1:3

Particulars	DPC 1:3 (mg)	Drug present (mg)
Estimated value	80	19.17
Calculated value	83.44	20

Table 4: Composition of different formulations of Dicyclomine hydrochloride oral disintegrating tablets

Ingredients (mg/tablet)	F1	F2	F3	F4	F5	F6	F7	F8	F9
DPC 1:3 equivalent to	83.44	83.44	83.44	83.44	83.44	83.44	83.44	83.44	83.44
20 mg of drug	102.56	96.56	90.56	102.56	96.56	90.56	102.56	96.56	90.56
Mannitol									
Avicel PH 101	90	90	90	90	90	90	90	90	90
Crosscarmellose sodium	6	12	18	-	-	-	-	-	-
Sodium starch glycolate	-	-	-	6	12	18	-	-	-
Crospovidone	-	-	-	-	-	-	6	12	18
Aspartame	6	6	6	6	6	6	6	6	6
Vanilla	3	3	3	3	3	3	3	3	3
Aerosol	6	6	6	6	6	6	6	6	6
Magnesium Stearate	3	3	3	3	3	3	3	3	3



Pure drug P

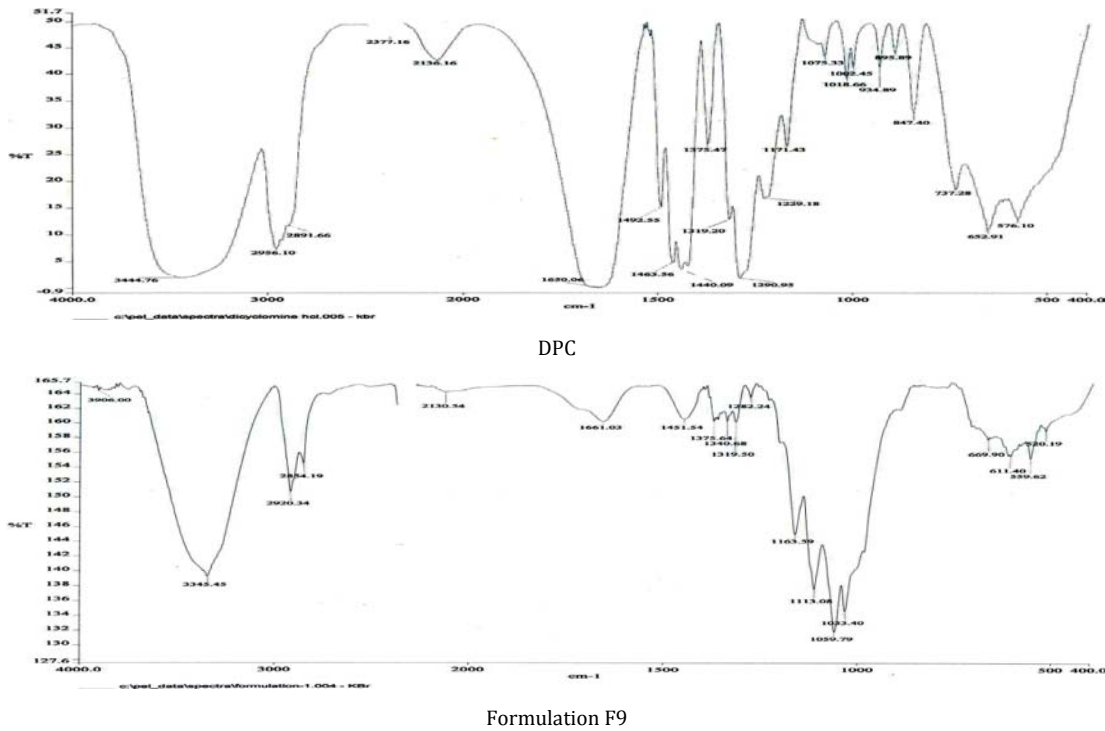


Fig. 2: FTIR spectra of pure drug, DPC and formulation F9

Table 5: Evaluation of pre compression parameters for various batches of ODTs

Formulation No.	Angle of repose	Loose bulk density (LBD) (g/ml)	Tapped bulk density (TBD) (g/ml)	Compressibility index (%)
F1	25.76 ± 1.32	0.254 ± 0.005	0.313 ± 0.013	18.84 ± 0.75
F2	27.35 ± 1.41	0.284 ± 0.004	0.342 ± 0.011	16.95 ± 1.63
F3	26.42 ± 1.78	0.252 ± 0.003	0.319 ± 0.014	21.00 ± 1.33
F4	27.42 ± 1.52	0.244 ± 0.009	0.295 ± 0.012	17.28 ± 1.48
F5	28.12 ± 1.57	0.239 ± 0.006	0.305 ± 0.016	20.95 ± 0.78
F6	26.12 ± 1.73	0.284 ± 0.006	0.342 ± 0.015	16.95 ± 0.61
F7	31.15 ± 1.38	0.301 ± 0.001	0.377 ± 0.018	20.15 ± 1.41
F8	30.26 ± 1.34	0.298 ± 0.007	0.391 ± 0.019	23.78 ± 1.76
F9	32.35 ± 1.81	0.303 ± 0.003	0.375 ± 0.011	19.20 ± 1.58

Table 6: Evaluation of post compression parameters for various batches of ODTs

Formula - tion No.	Hardness (kg/cm <sup>2</sup> )	Friability (%)	Weight variation	Thickness (mm) ±S.D	Disintegration time (sec)	In vitro dispersion time (sec)	Wetting time (sec)
F1	2.7 ± 0.10	0.53 ± 0.61	Passes	3.75 ± 0.15	28.47	29.32	35.97
F2	2.6 ± 0.24	0.42 ± 0.41	Passes	3.64 ± 0.43	25.07	24.89	31.43
F3	2.7 ± 0.14	0.49 ± 0.12	Passes	3.86 ± 0.27	19.55	20.13	26.45
F4	2.6 ± 0.12	0.51 ± 0.21	Passes	3.76 ± 0.18	38.85	41.41	50.25
F5	2.7 ± 0.35	0.41 ± 0.21	Passes	3.68 ± 0.23	34.84	35.32	43.15
F6	2.8 ± 0.13	0.48 ± 0.13	Passes	3.79 ± 0.42	35.86	36.01	46.76
F7	2.7 ± 0.34	0.52 ± 0.41	Passes	3.68 ± 0.27	19.54	20.45	26.24
F8	2.8 ± 0.25	0.47 ± 0.12	Passes	3.78 ± 0.17	14.02	14.78	19.29
F9	2.7 ± 0.12	0.46 ± 0.35	Passes	3.87 ± 0.19	9.85	10.04	14.27

Estimation of drug content uniformity in optimized formulation F9

Table 7: Estimation of drug content uniformity in optimized formulation F9

Peak #	Ret. Time (min)	Area	% Of drug content	Drug present (mg)
A1	2.403	119948	100	20
B3	2.395	118142	98.49	19.69

Table 8: Percentage of drug content uniformity in optimized formulation F9

Tablet formulation	% Of drug content	Estimated value (mg)	Calculated value (mg)
F9	20	98.49 %	19.69

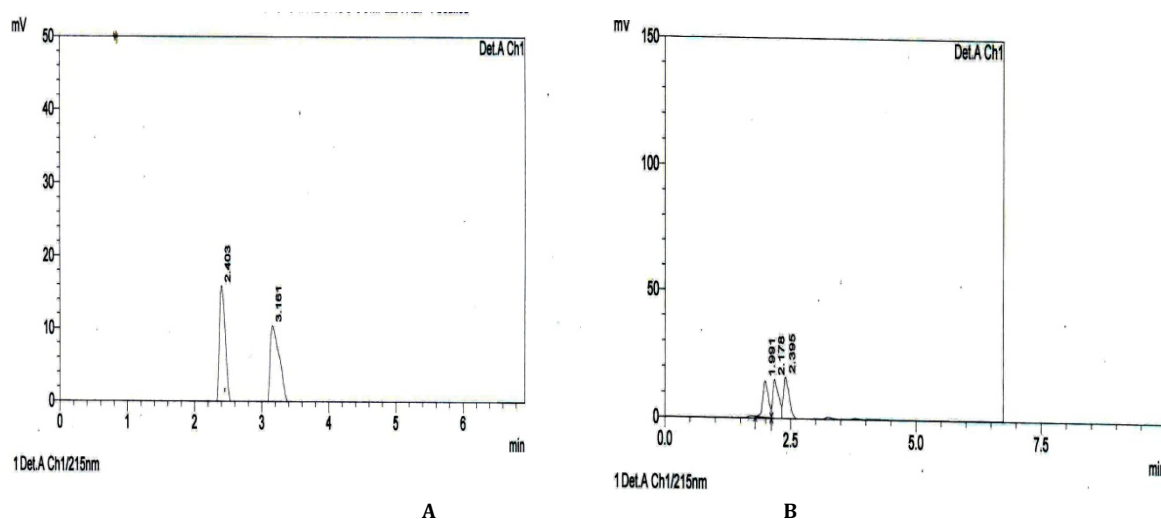


Fig. 3: Chromatogram of pure drug (A) and optimized formulation F9 (B)

#### Estimation of drug content in DPC 1:3 by HPLC method

HPLC method was developed for the testing of drug content in DPC 1:3.

#### Chromatographic system.<sup>8</sup>

- A stainless steel column 15 cm x 4.6 mm, packed with octylsilane chemically bonded to porous silica (5 μm),
- Mobile phase: a mixture of 70 volumes of 0.02 M phosphate buffer pH 7.5 prepared by dissolving 2.72 g of monobasic potassium phosphate in 450 ml of water, adjusting the pH to 7.5 ± 0.1 with 10 per cent w/v solution of sodium hydroxide, diluting to 500 ml with water and 30 volumes of acetonitrile,
- Flow rate: 1 ml per minute,
- Spectrophotometer set at 215 nm,
- A 20 μl loop injector.

#### Method

- A. Dissolve the 20 mg of pure drug (dicyclomine hydrochloride) in 100 ml of 0.1 N HCl and shake for 15 min. filter and inject 20 μl of filtrate in a column with the help of 20 μl loop injector and record the chromatogram.
- B. Dissolve the 80 mg of DPC 1:3 in 100 ml of 0.1 N HCl and shake for 15 min. filter and inject 20 μl of filtrate in a column with the help of 20 μl loop injector and record the chromatogram.
- C. Compare the retention time and area of the peaks in both the chromatograms and calculate the amount of drug present in DPC 1:3 (see table No. 2).

On the basis of observations shown in table No. 3, 83.44 mg of DPC 1:3 was finalized for the formulation which has equivalent to the dose of dicyclomine hydrochloride (20 mg).

#### Formulation of oral disintegrating tablets (ODTs)

Direct compression method and the various formulae used in the study are shown in Table No 2. The dicyclomine hydrochloride: Eudragit E-100 complex (DPC) and different excipients incorporated were Avicel PH 101 and Mannitol (as diluent), Superdisintegrants such as, Crosscarmellose sodium, Crospovidone and Sodium starch glycolate were used in different concentrations, Aspartame (as sweetener), Vanilla (flavouring agent) Aerosil and Magnesium stearate (as lubricant) were passed through sieve # 44. All the above ingredients were properly mixed together (in a poly-bag). The powder blend was compressed into tablets on a ten-station rotary punch tableting machine (Shakti Pharmatech Pvt. Ltd, Ahmedabad) using 9.5 mm flat-shaped punches.

#### Evaluation of ODTs

##### Pre Compression Parameters.<sup>9</sup>

##### Bulk density ( $D_b$ )

It is the ratio of powder to bulk volume. The bulk density depends on particle size distribution, shape and cohesiveness of particles. Accurately weighed quantity of powder was carefully poured into graduated measuring cylinder through large funnel and volume was measured which is called initial bulk volume. Bulk density is expressed in gm/cc and is given by,

$$D_b = M / V_o$$

Where,  $D_b$  = Bulk density (gm/cc)

M is the mass of powder (g)

$V_o$  is the bulk volume of powder (cc)

##### Tapped density ( $D_t$ )

Ten grams of powder was introduced into a clean, dry 100 ml measuring cylinder. The cylinder was then tapped 100 times from a constant height and tapped volume was read. It is expressed in gm/cc and is given by,

$$D_t = M / V_t$$

Where,  $D_t$  = Tapped density (gm/cc)

M is the mass of powder (g)

$V_t$  is the tapped volume of powder (cc)

##### Angle of repose ( $\theta$ )

It is defined as the maximum angle possible between the surface of pile of the powder and the horizontal plane. Fixed funnel method was used. A funnel was fixed with its tip at a given height (h), above a flat horizontal surface on which a graph paper was placed. Powder was carefully poured through a funnel till the apex of the conical pile just touches the tip of funnel. The angle of repose was then calculated using the formula,

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

Where,  $\theta$  = angle of repose

h = height of pile, r = radius of the base of the pile.

##### Carr's Index (I)

It indicates the ease with which a material can be induced to flow. It is expressed in percentage and is given by

$$I = \frac{D_t \cdot D_b}{D_t} \times 100$$

Where,  $D_t$  is the tapped density of the powder.

$D_b$  is the bulk density of the powder.

### Post Compression Parameters

#### Hardness test

It is the tensile strength of tablets expressed in kg/cm<sup>2</sup>. It is the pressure required to break the tablet into two halves by compression.<sup>10</sup>

#### Weight Variation

Weight variation test is done with 20 tablets. It is the individual variation of tablet weight from the average weight of 20 tablets.<sup>11</sup>

#### Friability

This test is performed to know the effect of friction and shocks on tablets. Preweighed sample of tablets were placed in the friabilator (Roche friabilator), and operated for 100 revolutions. Tablets were dusted and reweighed. The test complies if tablets not loose more than 1% of their weigh.<sup>12</sup>

#### Thickness

The thickness of three randomly selected tablets from each formulation was determined in mm using a vernier caliper (Mitutoyo Corporation, Japan). The average values were calculated.

#### Drug content uniformity of selected formulation by HPLC method

Five tablets were crushed and from this, quantity equivalent to 20 mg of dicyclomine hydrochloride was dissolved in suitable quantity of 0.1 N HCl. Solution was filtered and diluted and analyzed for drug content as per procedure mentioned in estimation of drug content in DPC 1:3 by HPLC method.<sup>8</sup>

#### Disintegration Time

The disintegration time was measured using disintegration test apparatus. One tablet was placed in each tube of the basket. The basket with the bottom surface made of a stainless-steel screen (mesh no. 10) was immersed in water bath at 37 ± 20C. The time required for complete disintegration of the tablet in each tube was determined using a stop watch. To be complied with the pharmacopoeial standards, dispersible tablets must disintegrate within 3 min when examined by the disintegration test for tablets.<sup>13</sup>

#### In vitro dispersion time

For determination of in vitro dispersion time, one tablet was placed in a beaker containing 10 ml of pH 6.8 phosphate buffer at 37 ± 0.5 °C and the time required for complete dispersion (with mild shaking) was determined.<sup>14</sup>

#### Wetting Time

This method will duplicate the *in vivo* disintegration, as the tablet is motionless on the tongue. Wetting time was measured by placing a tablet on a piece of tissue paper folded twice, and was placed in a small petri dish containing 6 ml of simulated saliva pH 6.8 and the time for complete wetting was measured.<sup>15</sup>

#### Stability Studies

Stability studies of pharmaceutical products were done as per ICH guide lines. These studies are designed to increase the rate of chemical or physical degradation of the drug substance or product by using exaggerated storage conditions.

Method: Selected formulations were stored at different storage conditions at elevated temperatures such as 25°C ± 2°C / 60% ± 5% RH, 30°C ± 2°C / 65% ± 5% RH and 40°C ± 2° / 75% ± 5% RH for 90 days. The samples were withdrawn at intervals of fifteen days and

checked for physical changes, hardness, friability, drug content and percentage drug release.

## RESULTS AND DISCUSSION

### Compatibility studies

The incompatibility between the drug and polymer were studied by FTIR spectroscopy. The spectral data of pure drug and drug-polymer mixtures are presented in Fig. 2. The results indicate that there was no chemical incompatibility between drug and polymer used in the formulation of taste masked granules.

### Characterization of DPC

#### In vitro taste evaluation

*In vitro* taste evaluation was conducted and results were shown in table No. 1. On the basis of observations Drug polymer ratio 1:3 was finalized for further study which shows 4.9 ± 0.31% of drug release.

#### Estimation of drug content in DPC 1:3 by HPLC method

Estimation of drug content present in DPC 1:3 was carried out and results were shown in table No. 2. The amount of the drug present was found to be 19.17 mg in 80 mg of DPC (95.87 %).

On the basis of observations shown in table No. 3, 83.44 mg of DPC 1:3 was finalized for the formulation which was equivalent to the dose of dicyclomine hydrochloride (20 mg).

### Pre Compression Parameters

The granular properties like Loose bulk density, Tapped bulk density, Compressibility index and angle of repose, for the batches F1-F9, were determined and the results were reported, as shown in Table No. 5.

#### Hardness test

The hardness test was carried out for each batch of all formulations F1 to F9 and results were shown in Table No. 6. All the formulations show hardness in ranged between 2.6 to 2.8 Kg/cm<sup>2</sup>.

#### Weight Variation

The weight variation test was conducted for each batch of all formulations F1 to F9 as per I.P and the all the formulations were passes the test (± 10%).

#### Friability

The friability test for all the formulations were done as per the standard procedure I.P. The results of the friability test were tabulated in Table No. 6. The data indicates that the friability was less than 1% in all formulations ensuring that the tablets were mechanically stable.

#### Thickness

The thickness of the tablets was found to be almost uniform in all formulations F1 to F9. The thickness was found to be in the range of 3.64 to 3.87 mm. None of the formulations (F1 to F8) showed a deviation. Hence, it is concluded that all the formulations complied the thickness test and the results are shown in Table No 6.

#### Drug content uniformity of selected formulation by HPLC method

Estimation of drug content uniformity of selected formulation i.e. optimized formulation F9 was carried out and the result was found to be 98.49 % which is within the I.P. limit.

#### Disintegration Time

Disintegration test was conducted as per the I.P. procedure for each batch of all formulations F1 to F9 and the results were tabulated in table No. 6. All the formulations (F1 to F9) shown disintegrating time within 1 min (9.85 to 38.85 sec). Optimized formulation F9 shows less than 10 sec.

**In vitro dispersion time**

*In vitro* dispersion time was conducted for each batch of all formulations F1 to F9 and the results were tabulated in table No. 6. All the formulations (F1 to F9) shown *in vitro* dispersion time within 1 min (41.41 to 10.04 sec). Optimized formulation F9 shows less than 11 sec.

**Wetting Time**

Wetting time was conducted for each batch of all formulations F1 to F9 and the results were tabulated in table No. 6. All the formulations (F1 to F9) shown wetting time within 1 min (50.25 to 14.27 sec). Optimized formulation F9 shows less than 15 sec.

**CONCLUSION**

In the present work, an attempt was made to develop taste masking of Dicyclomine Hydrochloride by polymer carrier system and formulation of oral disintegrating tablets. From the study conducted that, amongst the various ratios of DPC were formulated (solvent evaporation method), DPC 1:3 was selected for the formulation and tablets that were formulated (direct compression) using Crospovidone exhibited quicker disintegration of tablets than compared to those of Crosscarmellose sodium and Sodium starch glycolate.

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