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FORMULATION DEVELOPMENT AND EVALUATION OF RAPID RELEASE ORAL FILM OF DONEPEZIL HCl

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ABSTRACT :

The present study deals with the formulation and evaluation of rapid release oral film of Donepezil Hydrochloride which is a specific non-competitive reversible inhibitor of acetyl cholinesterase (AChE) used in the treatment of Alzhiemer's disease. The objective of preparing Donepezil HCl rapid release film was to dissolve or disintegrate the film in few seconds and release the drug in oral cavity for rapid therapeutic effect due to a well supplied vascular and lymphatic drainage. Donepezil HCl films were prepared by solvent casting technique using film forming polymer HPMC E-15, different types of disintegrants such as maize starch, pregelatinized starch and superdisintegrants such as sodium starch glycolate, croscarmellose sodium and crospovidone. Triacetin was incorporated as plasticizer to improve the flexibility of films, glycerin as emollient, mannitol as diluent to provide good mouth feel and aspartame as sweetener. The prepared films were evaluated for weight variation, thickness, surface pH, folding endurance, drug content, disintegration time and *in vitro* dissolution studies by Pharmaceutical standard methods. Formulation F5 is considered as the best formulation as it showed good tensile strength (39.52 N/cm^2), percentage elongation (11.83%), maximum drug content (99.75%), rapid disintegration time (20 seconds) and maximum drug release (99.86%) at the end of 10 minutes. The study concludes that rapid release oral films of Donepezil Hydrochloride can be considered suitable for clinical use in the treatment of Alzhiemer's disease, where a quicker onset of action along with the convenience of administration with higher therapeutic efficacy and bioavailability was desirable.

Keywords: Alzheimer's disease, Donepezil HCl, HPMC E-15, Rapid dissolving film, Solvent casting method.

INTRODUCTION:

The oral route widely preferred for its convenience, cost-effectiveness and ease of drug administration, presents challenges due to swallowing difficulties, particularly among pediatric and geriatric patients who fear choking. [1] Difficulty in swallowing or dysphagia is seen to afflict nearly 35% of the general population. In some cases such as motion sickness, sudden episodes of allergic attack or coughing, fear of choking and unavailability of water, the swallowing of tablets or capsules may become difficult. To overcome these difficulties, several Fast-Dissolving Drug Delivery Systems have been developed. Therefore, in the late 1970s, Fast-Dissolving Drug Delivery Systems (FDDS) were developed as a substitute for tablets, capsules and syrups for patients in the pediatric and elderly populations. These systems are made up of solid dosage forms that dissolve and disintegrate fast in the oral cavity without the need for water. [2] Orally fast-dissolving film is a new drug delivery system for the oral delivery of drugs. It was developed based on the technology of the transdermal patch.

The delivery system consists of a very thin oral strip, which is simply placed on the patient's tongue or any oral mucosal tissue, instantly wet by saliva. The film rapidly hydrates and adheres to the site of application. It will then rapidly disintegrates and dissolves to release the medication for oromucosal and intragastric absorption. Thin films are similar in size, shape and thickness to a postage stamp. They are usually intended for oral administration.[3] Fast-dissolving films are used to improve drug delivery and are most suitable for drugs that undergo rapid first-pass metabolism. Bioavailability can be achieved by lowering dosage frequency to reduce plasma peak levels, which minimizes side effects and increases cost-effectiveness. When drugs are delivered by mouth, certain issues can develop, including first-pass metabolism and enzymatic degradation in the GI tract. For several drug classes, these issues can be resolved by administering the medication through oral mucosa. [4]

Donepezil is a piperidine-based, reversible acetylcholinesterase inhibitor developed for the symptomatic treatment of Alzheimer's disease.The objective of preparing Donepezil HCl rapid release film was to dissolve or disintegrate the film in few seconds and release the drug in oral cavity for rapid therapeutic effect due to a well supplied vascular and lymphatic drainage.

MATERIALS AND METHODS:

MATERIALS:

Donepezil HCl was purchased from Vasudha Pharma Chem. Ltd, India. HPMC E15 was procured from Taian Ruitai Cellulose, China, Triacetin was procured from Mdk Chemtex Private Limited, India, Maize starch, Pregelatinized starch were procured from Universal Starch Chem Allied Ltd, India. Sodium starch glycollate was procured from Maruti Chemicals, India. Croscarmellose sodium was procured from J.R Pharma, India. Crospovidone was procured from Boai NKY Pharmaceuticals, Ltd, China. Remaining chemicals used were of analytical grade.

PREPARATION OF RAPID RELEASE ORAL FILM OF DONEPEZIL HCl:

The films were prepared by solvent casting method. The polymer solution was prepared by dissolving the required quantity of polymer in 100ml of distilled water in a container. To that polymer solution, plasticizer, super disintegrants and sweetening agents are added and mixed well. In another container, accurately weighed quantity of Donepezil HCl was taken and dissolved in 30 ml of distilled water. The prepared drug solution was transferred to the container having polymeric solution and added slowly with continuous stirring. The resultant solution was slowly poured to cast as a film on the petri dish and allowed to dry for 3 hours at 50˚C. The formed films were carefully removed from the petri dish and cut into desired size of 3×2 cm^2 per strip each containing 5mg drug. The dried films were packed individually into an aluminium pouch and sealed. Formulation composition of rapid release oral film of Donepezil HCl was shown in table 1.

Table: 1 Composition of Rapid Release Oral Film of Donepezil HCl Formulations

INGREDIENTS	QUANTITY PER ORAL FILM (mg)				
	F1	F2	F3	F4	F5
Donepezil HCl	5.00	5.00	5.00	5.00	5.00
HPMC E15	20.00	20.00	20.00	20.00	20.00
Glycerin	5.00	5.00	5.00	5.00	5.00
Triacetin	0.15	0.15	0.15	0.15	0.15
Mannitol	5.35	5.35	5.35	5.35	5.35
Maize starch	4.00	-	-	-	-

Pregelatinized starch	-	4.00	-	-	-
Sodium starch glycollate	-	-	4.00	-	-
Croscarmellose sodium	-	-	-	4.00	-
Crospovidone	-	-	-	-	4.00
Aspartame	0.50	0.50	0.50	0.50	0.50
Purified water	Qs	Qs	Qs	Qs	Qs
Average weight of the strip	**40.00**	**40.00**	**40.00**	**40.00**	**40.00**

PREFORMULATION STUDY: [5]

ORGANOLEPTIC PROPERTIES: [6]

a) Color: A small quantity of Donepezil HCl was taken in a butter paper and viewed in a well –illuminated place.

b) Taste and Odor: A very small quantity of Donepezil HCl was used to assess the taste with the help of tongue as well as smelled to assess the odor.

SOLUBILITY ANALYSIS: [7]

Donepezil HCl was tested for solubility in a variety of solvents like, water, chloroform, glacial acetic acid, ethyl acetate and n-hexane.

MELTING POINT DETERMINATION: [8]

The melting point was determined by placing a small amount of Donepezil HCl in a capillary tube that was closed at one end and placed in a melting point apparatus. The temperature at the time when the substance completely melts was noted and the melting point was determined.

DRUG - EXCIPIENT COMPATIBILITY STUDY: [9]

The excipients which are found to be physically and chemically compatible with the drug should be incorporated in the film formulation. The excipients and drug were taken in different ratios and homogeneously mixed with a mortar and pestle for 10 min. and the powder mixture was placed in petriplate. These petriplates were kept in the dessicator at 45- 60°C for a period of 15 days. The samples were evaluated at the initial stage and after 7 days and 15 days of exposure for any changes like liquefaction, color, odor or gas formation.

POST FORMULATION STUDIES: [10]

GENERAL APPEARANCE:

The formulated films were evaluated for organoleptic characters such as color and odor. The film should be free from cracks and the prepared films were assessed for flexibility, homogeneity, transparency and surface roughness.

THICKNESS: [11]

Thickness can be measured by using calibrated digital vernier caliper. Anvil of the thickness gauge was lifted and the film (3×2 cm^2) was inserted after making sure that pointer was set to zero. The film was held on the anvil and the reading on the dial was noted down.

WEIGHT VARIATION TEST:

This test was carried out by taking 3×2 cm^2 of the five film. The weight of each film was taken individually using electronic balance. The average weight is calculated. The individual weight should not deviate significantly from the average weight.

TENSILE STRENGTH: [12]

The tensile strength was defined as the maximum load force required to break the film. The tensile strength of oral films were measured using a texture analyser. Tensile strength was determined by using the following formula.

$$\text{Tensile strength} = \frac{\text{Load at break}}{\text{Strip thickness} \times \text{Strip width}} \text{ X } 100$$

FOLDING ENDURANCE:

A film was cut evenly and repeatedly folded at the same spot until it breaks. For each formulation, six samples were examined.

PERCENTAGE ELONGATION: [13]

The increase in the length of the film when it is pulled under standard conditions of stress just before the point of break is known as percentage elongation. Randomly 3 films were selected and initial length was measured. Films were pulled manually unit it breaks. Then final length was observed and average percentage elongation was determined. The percentage elongation of the film was determined by the following formula.

Percentage elongation = Increase in length of strip / Initial length of strip × 100

SURFACE pH: [14]

The surface pH was determined by using the pH meter. The film was allowed to swell by keeping it in contact with distilled water for 1 h at room temperature and the pH was recorded.

PERCENTAGE MOISTURE UPTAKE: [15]

The percentage moisture uptake of films was calculated by exposing it to an atmosphere with a relative humidity of 75% at room temperature for seven days. Moisture absorption is calculated using the following formula.

$$\%\text{Moisture uptake} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

PERCENTAGE MOISTURE LOSS:

The original weight of the film was determined first and then the film was placed in a dessicator containing calcium chloride for three days to determine the percentage moisture loss. The films were removed and weighed again after three days and the percentage moisture loss was calculated using the formula:

$$\%\text{ Moisture loss} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

DISINTEGRATION TIME: [16]

The *in vitro* disintegration time of the oral film formulations (3×2 cm^2) was determined using a disintegration test apparatus with 900 ml of distilled water at 37.0 ± 0.5°C. The disintegration time was defined as the time taken for oral film to completely disintegrate with no solid residue remaining on the screen.

DRUG CONTENT: [17]

A film of size 3×2 cm^2 is cut and placed in volumetric flask containing 30 ml of phosphate buffer pH 6.8. This is then shaken in a mechanical stirrer for 1 hr to get a homogeneous solution and filtered. From this suitable dilution was prepared and the solution was analysed at 286nm using phosphate buffer pH 6.8 as blank.

Drug content = Absorbance of sample / Absorbance of standard x 100.

***IN VITRO* DISSOLUTION STUDY:** [18]

In vitro drug dissolution study was carried out using Type-5 USP dissolution apparatus using 900 ml of pH 6.8 phosphate buffer as dissolution medium. The dissolution test was carried out at 50 rpm at 32 ±0.5ºC. The prepared oral film was cut in to a size of 3×2 cm^2 and attached to a stainless-steel disk, which is then placed on the bottom of the vessel, directly under the paddle containing phosphate buffer medium. 1 mL of sample was taken at specific time intervals (2-10 minutes). An equal volume of the dissolution medium was replaced in the vessel after taking sample to maintain sink condition. The concentration of the drug was determined by

UV-Vis spectrophotometer at 286 nm. The percentage of drug release was calculated and plotted against various time intervals.

FT-IR SPECTROSCOPY STUDIES: [19]

Fourier transform infrared (FT-IR) study was used to determine the interactions between the drug and excipients. The sample was prepared and mixed with suitable quantity of potassium bromide. About 50 mg mixture was compressed to form transparent pellet using hydraulic press at 10 tons pressure. It was scanned between 4000-400cm^1 in a Shimadzu FT-IR spectrophotometer. The IR spectrum of pure drug and best formulation was compared to identify the appearance or disappearance of peak if any.

DIFFERENTIAL SCANNING CALORIMETRY ANALYSIS: [20]

Donepezil HCl and the best formulation of Donepezil HCl film were investigated by Differential Scanning Calorimetry (DSC) to characterize the thermal properties of oral films. DSC thermograms were recorded using a differential scanning calorimeter (DSC-60 plus, Shimadzu, Japan). An accurately weighed sample (2-4 mg) of pure drug and the best formulation of Donepezil HCl was heated in hermetically sealed aluminium pans under nitrogen purge (100 ml/min) over a temperature range of 25˚C-300˚C at a constant rate of 10˚C/min and DSC thermograms were recorded and studied.

STABILITY STUDIES: [21]

Stability study for the best formulation of rapid release oral film of Donepezil HCl (short term study) was performed at 40 ± 2°C /75% ± 5% RH for one month. Samples were analyzed for appearance, surface pH, disintegration and *in vitro* dissolution studies during initial period and at an interval of 15 and 30 days.

RESULTS AND DISCUSSION:

PREFORMULATION STUDIES:

The color of Donepezil HCl was found to be white to cream crystalline powder and no characteristic odor was observed in the study and the taste was found to be bitter. Donepezil HCl showed similar color, odor and taste as per USP.

The solubility analysis of drug (API) revealed that Donepezil HCl was soluble in water, chloroform and glacial acetic acid. Slightly soluble in ethanol, acetonitrile and insoluble in ethyl acetate and in n- hexane. The melting point of Donepezil HCl was found to be 212˚C, which complies with USP specification.

In the drug - excipients compatibility study, it was observed that there was no characteristic change found between the drug and excipients. Thus it was concluded that the excipients selected for the formulation were compatible with Donepezil HCl and suitable for formulation development.

EVALUATION OF DONEPEZIL HCl RAPID RELEASE ORAL FILMS:

Table 2: Evaluation Parameters of Rapid Release Oral Films of Donepezil HCl

FORMULATION CODE	WEIGHT (mg)	THICKNESS (µm)	FOLDING ENDURANCE	TENSILE STRENGTH (N/cm^2)	PERCENTAGE ELONGATION
F1	41.1±0.12	42 ± 0.32	54 ± 2.1	30.93 ± 2.11	10.52 ± 2.32
F2	42.2± 0.32	79 ± 2.0	43 ± 5.2	33.34 ± 3.96	10.96 ± 3.56
F3	41.9± 0.14	79 ± 3.2	46 ± 3.4	37.71 ± 2.33	10.98 ±2.43
F4	42.1± 0.23	81 ± 1.8	52 ± 3.1	32.66 ± 6.88	9.96 ± 6.76
F5	41.3± 0.37	78 ± 2.6	68 ± 5.2	39.52 ± 4.84	11.83 ± 5.43
Marketed sample	50.3± 0.82	85 ± 2.2	37 ± 3.2	48.52 ± 1.63	12.63 ±1.52

***All the values are expressed as mean + SD, n=3**

Weight of Donepezil HCl rapid release oral films ranges from 41.1 ± 0.12 to 42.2 ± 0.32 mg. The results revealed that there was no significant variation found in the weight of films and hence it complies the weight variation test. The thickness value of all the formulations varied between

42 ± 0.32 to 81 ± 1.8 µm. The standard deviation values were low indicating uniformity in thickness for all formulations. The folding endurance varied between 43 ± 5.2 to 68 ± 5.2 times for all the formulations, which revealed good mechanical strength and elasticity for all the formulations which may be due to the addition of plasticizer. Tensile strength of all formulations ranges between 30.93 ± 2.11 to 39.52 ± 4.84 N/cm^2 for all the formulations. The results showed that percentage elongation ranges between 9.96 ± 6.76% to 11.83 ± 5.43% for all the formulations (Table -2). Formulation F5 showed maximum folding endurance, tensile strength and percentage elongation compared to other formulations.

Table 3: Evaluation Results of Rapid Release Oral Films of Donepezil HCl

FORMULATION CODE	PH	DISINTEGRATION TIME (sec)	DRUG CONTENT (%)
F1	7.25 ± 0.05	50 ± 0.16	98.95 ± 1.13
F2	7.30 ± 0.11	45 ± 0.09	99.00 ± 0.97
F3	7.32 ± 0.05	45 ± 0.12	99.50 ± 0.82
F4	7.30 ± 0.03	40 ± 0.16	99.50 ± 1.19
F5	7.25 ± 0.10	20 ± 0.12	99.75 ± 0.95
Marketed sample	7.28 ± 0.09	35 ± 0.56	100.75 ± 0.56

***All the values are expressed as mean + SD, n=3**

The surface pH of rapid release oral film of Donepezil HCl has been found in the range of 7.25 ± 0.05 to 7.32 ± 0.05, which is similar to salivary pH and hence the films will not cause any irritation to oral mucosa. All the rapid release oral film of Donepezil HCl have shown disintegration time of less than 1 minute. Formulation F5 showed better disintegration (20 ± 0.12 seconds) time than all other formulations and marketed product (35 ± 0.56 seconds). The drug content of rapid release oral film of Donepezil HCl was observed between 98.95% to 99.75 % (Table-3). The drug was evenly distributed throughout each film. Formulation F5 containing Crospovidone as superdisintegrant showed maximum drug content (99.75% ±0.95) amongst all other formulations.

PERCENTAGE MOISTURE UPTAKE AND PERCENTAGE MOISTURE LOSS:

Table 4: Percentage Moisture Uptake and Percentage Moisture Loss Study of Rapid Release Oral Film of Donepezil HCl

FORMU-LATION CODE	INITIAL WEIGHT (mg)	FINAL WEIGHT (mg)	PERCENTAGE MOISTURE UPTAKE(%)	INITIAL WEIGHT (mg)	FINAL WEIGHT (mg)	PERCENTAGE MOISTURE LOSS (%)
F1	46.2±1.8	46.8±1.4	1.29	46.2±1.8	45.6±0.7	1.29
F2	45.0±2.1	45.6±1.2	1.33	45.0±2.1	43.8±1.1	2.67
F3	46.1±1.8	47.1±0.8	2.17	46.1±1.8	45.7±1.6	0.89
F4	44.5±1.3	45.1±1.8	1.35	44.5±1.3	43.5±0.8	3.12
F5	44.9±1.7	45.7±2.1	1.79	46.2±1.8	45.6±1.5	1.29

***All the values are expressed as mean + SD, n=3**

In moisture uptake study of the developed films of Donepezil HCl, it was observed that the maximum moisture uptake was less than 2.17% which ensures less microbial contamination and bulkiness. In moisture loss study of the developed films of Donepezil HCl, it was observed that the maximum moisture loss was 3.12 % indicating that the formulations maintained their stability during the study period. Moisture loss of the different films were found to be ranging from 0.89 % to 3.12 % (Table-4).

***IN VITRO* DRUG RELEASE STUDY:**

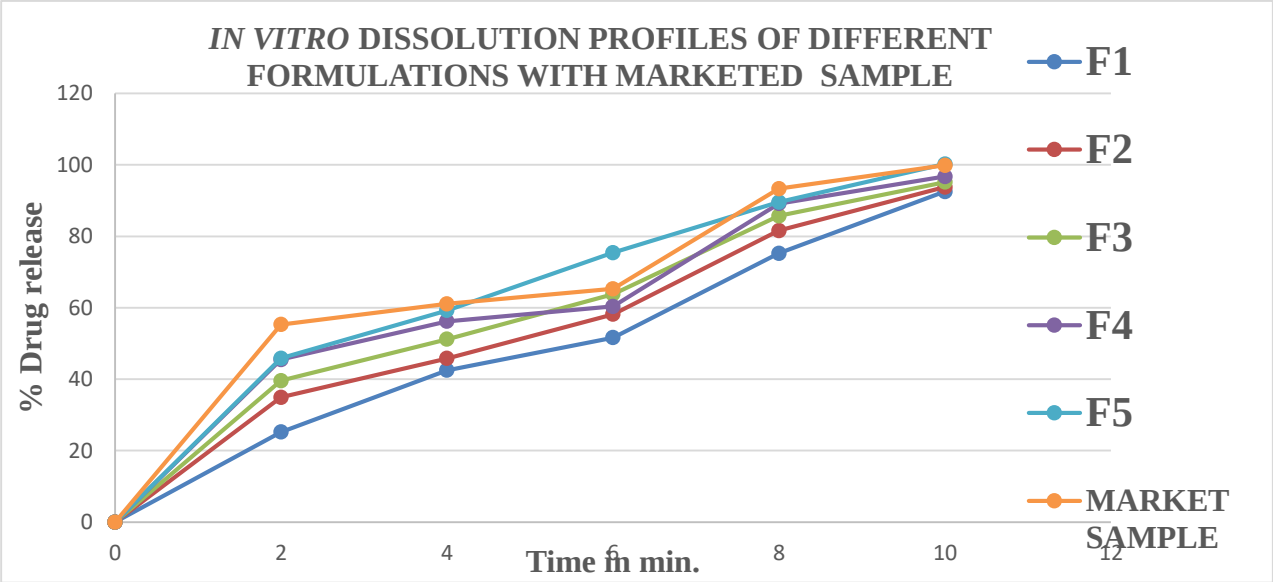

Figure 1: *In* vitro Drug Release Profiles of Rapid Release Oral Films of Donepezil HCl

Rapid release oral film of Donepezil HCl formulations (F1 to F5) preparedwith different type of disintegrants and superdisintegrants were subjected to *in vitro* drug release studies. Formulation F1 and F2 showed 92.52% and 93.78% of drug release at the end of 10 minutes. Formulation F3, F4 and F5 showed 95.16%, 96.76% and 99.86% of drug release at the end of 10 minutes respectively. The drug release profiles were shown in figure 1. Formulation F5 showed maximum drug release compared to other formulations.The order of increasing dissolution rate observed with rapid release oral film of Donepezil HCl was found to be DPH- F5> F4> F3> F2> F1.

COMPARATIVE *IN VITRO* DRUG RELEASE STUDIES OF BEST FORMULATION (F5) AND MARKETED SAMPLE:

Table 5: Comparative *In vitro* Dissolution Study of Formulation (F5) and Marketed Sample

TIME (Minutes)	PERCENTAGE DRUG RELEASE (%)	
	F5	MARKETED SAMPLE
2	55.30±0.1.5	45.84±1.2
4	61.09±1.2	59.23±0.7
6	65.28±0.3	75.41±1.3
8	93.34±1.6	89.56±1.1
10	99.86±0.9	100.23±1.4

***All the values are expressed as mean + SD, n=3**

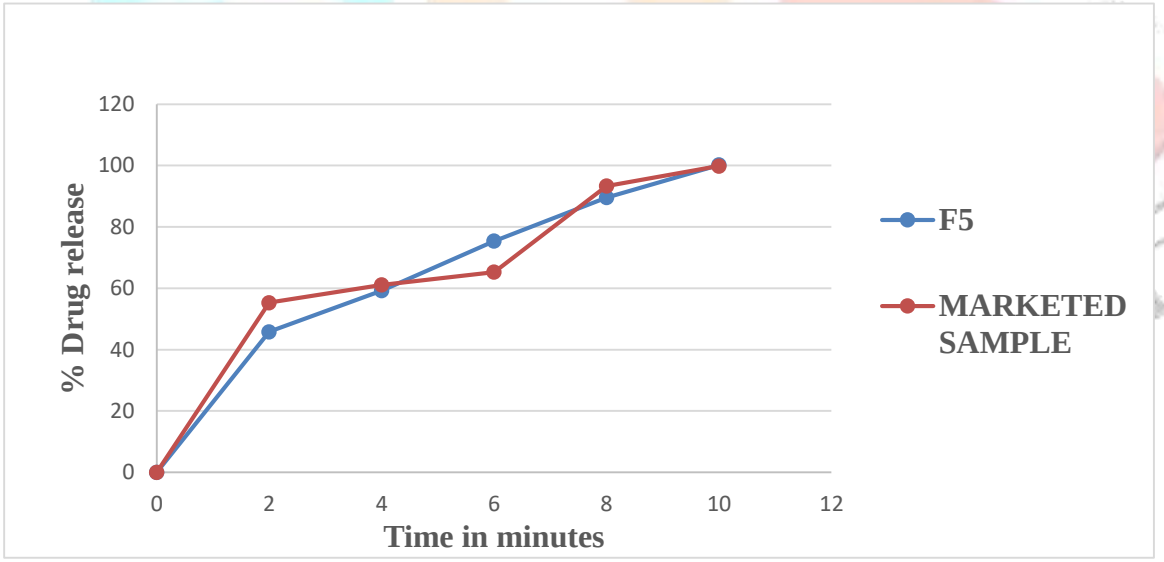

Figure 2: Comparative *In vitro* Dissolution Profile of Formulation (F5) and Marketed Sample

The drug release from the rapid release oral film of Donepezil HCl (F5) was found to be 99.86% at the end of 10 minutes and the drug release from the marketed sample was found to be 100.23 % at the end of 10 minutes (Table-5 and Figure -2). From the graph, it was found that the drug release from the marketed product is fairly matching with the drug release from the best formulation (F5) of rapid release oral film of Donepezil HCl.

FT – IR SPECTRAL STUDIES:

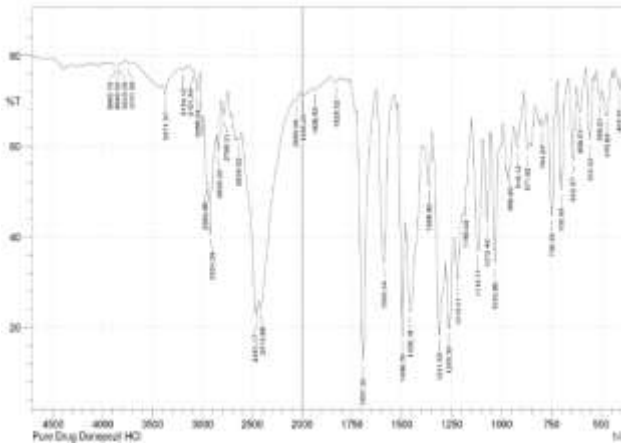

Figure 3: FT – IR Spectrum of Pure Donepezil HCl

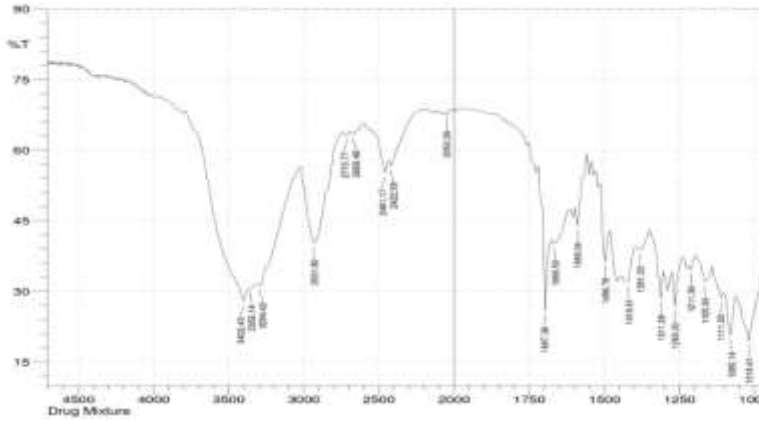

Figure 4: FT – IR Spectrum of Best Formulation (F5)

FT- IR spectral studies indicated that the drug is compatible with all the excipients. The FT – IR spectrum of the best formulation showed all the characteristic peaks of Donepezil HCl, thus confirming no drug interaction occurred with the excipients of the formulation (figure 3 and 4).

DIFFERENTIAL SCANNING CALORIMETRY (DSC) ANALYSIS:

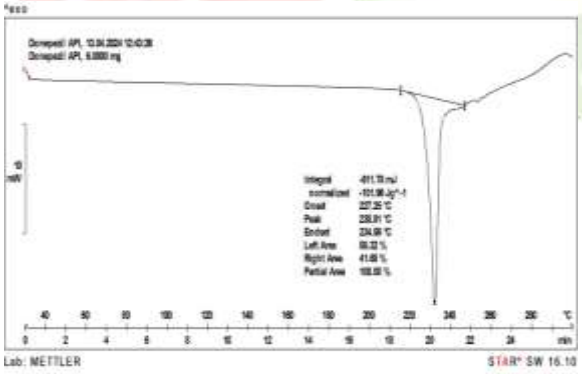

Figure 5: DSC Thermogram of Pure Donepezil HCl

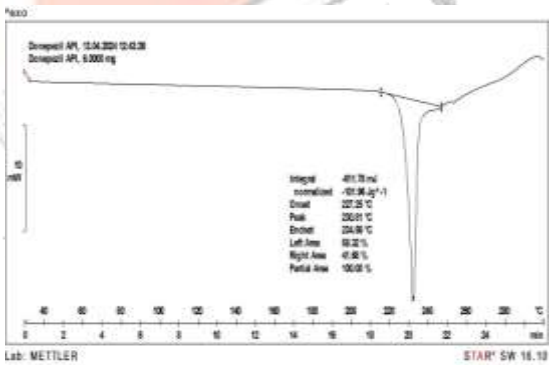

Figure 6: DSC Thermogram of Best formulation(F5)

DSC thermogram of Donepezil HCl showed a sharp endothermic peak at 230.8°C with normalized energy of 611.78 mJ corresponding to it's melting point (Figure - 5). The DSC curve of best formulation (F5) has an endothermic peak corresponding to the temperature range 165.99°C. These melting point values are consistent with the literature values of 150 to 165°C corresponding to the melting point of crospovidone (Figure – 6). These values and the accuracy of melting peaks indicate a high purity of the studied compounds. Hence the results revealed that there was no interaction occured between drug and best formulation (F5).

STABILITY STUDIES:

Table 6: Stability Study Data of Best Formulation (F5) of Rapid Release Oral Film of Donepezil HCl Stored at 40±2°C/75%± 5%RH

S. NO	PARAMETERS	STORAGE CONDITIONS: 40± 2°C/75%±5% RH		
		INITIAL PERIOD	AFTER 15 DAYS	AFTER 30 DAYS
1.	Appearance	Colorless, smooth, opaque and homogenous	No characteristic change	No characteristic change
2	Surface pH	7.32 ± 0.05	7.30 ± 0.03	7.32± 0.04
3	Disintegration time (sec.)	22.10 ± 2.01	22.99±1.99	23.95± 1.68
4	*In vitro* drug release at theend of 10 minutes (%)	99.41 ± 2.06%	98.41 ± 1.35%	98.02 ± 1.58%

***All the values are expressed as mean + SD, n=3**

Stability studies of best formulation (F5) revealed that there was no significant changes found in physical appearance, surface pH, disintegration time and *in vitro* dissolution time after 30 days. The color and texture of the product remained unchanged throughout the study period (Table 6). The stability study indicated that the formulation of rapid release oral film of Donepezil HCl was stable even after stored at 40 ± 2°C / 75% ± 5% RH for 30 days.

CONCLUSION:

Five formulations (F1 – F5) of rapid release oral film of Donepezil HCl were prepared by solvent casting method using different types of disintegrants such as maize starch, pregelatinized starch and superdisintegrants such as croscarmellose sodium, sodium starch glycolate and crospovidone for rapid drug release. The prepared films were found to be satisfactory when evaluated for thickness, weight uniformity, tensile strength, folding endurance, drug content and disintegration time. The surface pH of all films were found to be neutral which may not cause any irritation to oral mucosa.

Amongst all formulations, the formulation F5 prepared with crospovidone as superdisintegrant showed maximum tensile strength (39.52 N/cm^2), percentage elongation (11.83%), drug content (99.75%), rapid disintegration time (20 seconds) and maximum drug release (99.86%) at the end of 10 minutes. The study concluded that the rapid release oral film of Donepezil HCl could be successfully developed by solvent casting method.

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