IJPSR (2021), Volume 12, Issue 12 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 25 January 2021; received in revised form, 05 May 2021; accepted, 28 May 2021; published 01 December 2021

TASTE MASKING, DESIGN AND EVALUATION OF ORAL DISPERSIBLE TABLET OF ANTICHOLINESTERASE AGENT

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Keywords:

Orodispersible tablet, Donepezil HCl, Anticholinergic activity, Dementia

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ABSTRACT: This study aimed to determine for taste masking & design of Oro dispersible tablet of an anticholinesterase agent (Donepezil HCl) to achieve the patient compliance. Oral dispersible tablet prepared by compression method. The Anticholinergic activity assure by evaluation, drug dissolution, stability testing and standardize the oral dispersible tablet. On the basis of the preformulating and formulation study, the batch 10-F009 formulation would maintain stability and potency throughout the study period. Complete drug release was observed at gastric pH. Taste masking and rapid disintegration of tablets formulated in this investigation may possibly help in the administration of Donepezil HCL in a more palatable form without water. Finally, this formulation with once-daily dose is convenient for patients with the Alzheimer's disease and related dementia with good therapeutic activity and bioavailability.

INTRODUCTION: "Oro dispersible Tablet", by the European Pharmacopoeia which describes it as a tablet that can be placed in oral cavity where it disperses rapidly before swallowing. ODT products have been developed for numerous indications ranging from migraines (for which rapid onset of action is important) to mental illness (for which patient compliance is important for treating chronic indications such as depression and schizophrenia) [1]. Many orally administered drugs elicit a bitter taste. Today a change in patient attitude and development of taste masking technique has reversed this.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.12(12).6540-52

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.12(12).6540-52

Opinion. Patients now expect and demand formulations that are pleasantly, or at least tolerably, flavoured. This article reviews the earlier methodologies and approaches of taste masking of bitterness reduction [2]. ODT has become increasingly used in the life-cycle management of existing products. This is achieved by utilizing relatively new technology to extend the life of an established drug [1, 3]. These dosage forms dissolve or disintegrate in the oral cavity within seconds without the need for water or chewing.

These are useful for pediatric, geriatric and also dysphagia patients, leading to improved patient compliance [3]. Sensations of taste are elicited by the tongue and interpreted by the brain. The resulting sensation is transmitted to the brain by the ninth cranial (gloss opharyngeal) nerve. The tenth and twelfth cranial nerves participate in this sensory reaction, but their role is limited [4]. Psychophysical

studies suggest that human taste sensation can be divided into five distinct categories: amai (sweet), suppai (sour), shoppai (salty), nigai (bitter), and umami (glutamate). Taste buds are onion-shaped structures containing between 50 to 100 taste cells. Single taste cell can respond to a variety of taste sensations. The sensations of bitter and sweet tastes are initiated by the interaction of tast ants with G protein-coupled receptors (GPCRs) in the apical membranes of taste receptor cells (TRCs). TRCs are specialized epithelial cells with many neuronal properties, including the ability to depolarize and form synapses. TRCs are typically clustered in groups of ~100 within taste buds.

The convoluted apical surface of TRCs, which makes contact with the oral cavity, is rich in microvilli-containing GPCRs, ion channels, and other transduction elements. The basolateral aspect of TRCs contains ion channels and synapses with afferent taste nerves [5]. In the approaches of Taste Masking first one Sensory Approach in that using flavoring and sweetening agents, inhibiting bitterness, numbing of taste buds, Using CO_2 generating substance. Second one Complexation and Adsorption in that Sensations of taste are elicited by the tongue and interpreted by the brain. The resulting sensation is transmitted to the brain by the ninth cranial (glossopharyngeal) nerve. The tenth and twelfth cranial nerves participate in this sensory reaction, but their role is limited [4]. Psychophysical studies suggest that human taste sensation can be divided into five distinct categories: amai (sweet), suppai (sour), shoppai (salty), nigai (bitter) and umami (glutamate).

The human tongue contains over 9000 taste buds. The drug in solution directly and immediately contact and stimulate these taste buds. Taste buds are onion-shaped structures containing between 50 to 100 taste cells. Single taste cells can respond to a variety of taste sensations. The sensations of bitter and sweet tastes are initiated by the interaction of tast ants with G protein-coupled receptors (GPCRs) in the apical membranes of taste receptor cells (TRCs). TRCs are specialized epithelial cells with many neuronal properties, including the ability to depolarize and form synapses. TRCs are typically clustered in groups of - 100 within taste buds. The convoluted apical surface of TRCs, which makes contact with the oral cavity, is rich in microvilli-containing GPCRs, ion channels, and other transduction elements. The basolateral aspect of TRCs contains ion channels and synapses with afferent taste nerves [5]. In the approaches of Taste Masking first one Sensory Approach that Using flavoring and sweetening agents, inhibiting bitterness, numbing of taste buds, Using CO_2 generating substance. Second one Complexation and Adsorption in that Complexation using ion exchange resins, Formation of inclusion complexes with beta-cyclodextrin derivatives, Wax embedding of drugs.

Third, one Chemical Approach in that Formation of prodrugs, Formation of different salts. Fourth is Barrier Approach in that using microsphere or Microencapsulation, using viscosity modifier, Using Emulsion, Using liposomes [6, 7]. Alzheimer's disease (AD), also known in medical literature as Alzheimer disease, is the most common form of dementia. There is no cure for the disease, which worsens as it progresses and eventually leads to death.

Alzheimer is progressive neurodegenerative disorder that affects older individuals & is the most common cause of dementia. Atrophy of cortical & subcortical areas is associated with deposition of β-amyloid proteins in form of senile plaques & formation of neuro-fibrillary tangles. Marked cholinergic deficiency in brain, other neurotransmitter systems also affected. Comparison of a normal aged brain (left) and the brain of a person with Alzheimer's (right). Differential characteristics are pointed out [8].

MATERIALS AND CHEMICALS: Donepezil HCl Purchased from CHL, which is metabolized by CYP 450 isoenzymes 2D6 and 3A4 in the liver and also undergoes glucuronidation. The main metabolite, 6-O-desmethyl Donepezil HCl, has been reported to inhibit ache to the same extent as Donepezil HCl *in-vitro* [9, 10]. Mannitol (Pearlitol SD-200) from FMC, used as diluent for lyophilized preparations, sweetening agent, tablet and capsule diluents, tonicity agent [11]. Purolite C115 Kmr (Potassium Polacrilin) from Ion exchange resin Pvt. Ltd., it form cation exchange resin supplied as a dry powder [11]. Crospovidone purchased from ISP is used in a variety of pharmaceutical formulations, Special grades of pyrogen-free substance used in

the parenteral solution. Colloidal silicon dioxide is widely used in pharmaceuticals, cosmetics, and food products. Sucralose is used as a sweetening agent in beverages, foods, and pharmaceutical applications.11 Eudragit EPO purchased from Evonik, it is a cationic copolymer based on dimethya-minomethacryalate, buty methacrylate and methyl methacrylate [12]. Microcrystalline cellulose from Loba Chemie, Magnesium stearate from Dr. Paul Lohman, Eudragit RL 30 D from Evonik, Mint flavor DC 115 from Givaudan (India) Pvt. Ltd. Loss on Drying LOD test is designed to measure the amount of water and volatile matters, the quantity of moisture present in the API was determined by using a halogen moisture analyzer (5 min at 105 °C) and can be calculated as follows

LOD = (Initial Weight – Final Weight) × 100 / Initial Weight

Melting Point: It is one of the parameters to judge the purity of crude drugs. In the case of pure chemicals or phytochemicals, melting points are very Sharp and constant. They are described with a certain range of melting points.

Determination of λ_{max}: Aliquots of the working standard solution for Donepezil HCl were prepared by using methanol as a solvent and analyze the λ_{max} on UV Spectrophotometer in the range 200-400 nm. Reults show in **Fig. 1**.

Drug- Excipient Compatibility Study: Donepezil Hydrochloride (DH) and excipients are to be thoroughly mixed in the predetermined ratio given in below table and passed through the sieve No.40. Polymers used in the formulation are in liquid form / dry polymers were kept for stability conditions. The blend was filled in white coloured glass vials and are closed with grey rubber stoppers and sealed with aluminium seal, and charged into condition at 40 ºC/75% RH. Similarly, DH was also kept. Samples to be withdrawn for analysis within two days of sampling date as per the compatibility study plan [13].

TABLE 1: DRUG: EXCIPIENTS COMBINATION AND RATIO [13]

Sr. no.	Drug-Excipients combination	D:ERatio	D:E(gm)	15 Days/40 ºC/75% RH
M1	DH	-	-	1 Vial
M2	DH + Mannitol SD 200	1:1	2:2	1 Vial
M3	DH + Polacrilin Potassium	1:1	2:2	1 Vial
M4	DH + Cross Povidone XL 10	1:1	2:2	1 Vial
M5	DH + Aerosil	1:1	2:2	1 Vial
M6	DH+ Magnesium Sterate	1:1	2:2	1 Vial
M7	DH+ Sucralose NF	1:1	2:2	1 Vial
M8	DH+ Eudragit EPO	1:1	2:2	1 Vial
M9	DH+ Eudragit RL 30D	1:1	2:2	1 Vial
M10	DH+ HMR	1:1	2:2	1 Vial
M11	DH+ Calcium Silicate	1:1	2:2	1 Vial

XRD: X-ray diffraction is a versatile technique that reveals detailed information about the chemical composition and crystallographic structure of materials. X-ray Diffractometer is the instrument used for analysing the structure of materials from the scattering pattern produced when a beam of X-rays interacts with it. In order to obtain a good diffraction pattern of the sample must be ground to approximately <200 mesh size. The powdered sample must then be packed on the sample holder by backpressure technique and loaded the sample stage of the machine [14].

FTIR: Various techniques can be employed for placing the sample in the path of the Infra-red beam depending upon whether the sample is a gas, a liquid or a solid. Solids for the Infra-red spectrum may be examined as an alkali halide mixture. Sodium chloride and potassium bromide is commonly used. The sample (solid sample) is ground with KBr and is made into a disc after drying and then pressing it under pressure 250 Kg/cm^2 and elevated temperature. Also, a blank disc is prepared with pure potassium bromide, which may be placed in the path of the reference beam. It is even advisable to carry out grinding under an Infra-red lamp to avoid condensation of atmospheric moisture. Grinding is usually in agate mortar or pestle [14, 15].

Formulation Development:

Taste Masking of Donepezil Hydrochloride: Donepezil Hydrochloride (DH), a centrally acting reversible acetylcholinesterase inhibitor. The

purpose of this research was to formulate tasteless complexes of Donepezil HCl with a suitable agent. The tablets were formulated using 9.4 mm flat-shaped punches. Lubrication done with Magnesium Stearate (sieved through #60) for 5 min. The granules were then compressed by using Cadmach multi-station rotary tablet machine using 9.4 mm flat-shaped punches. The hardness was adjusted to 5-27 kg/cm^2.

TABLE 2: FORMULATION OF ORODISPERSIBLE TABLETS TASTE MASKING BY EUDRAGIT EPO, BATCH NO. 10-F001

Sr. no.	Ingredients	mg./tab
	Intragranular	
1	Donepezil Hydrochloride	10
2	PVP K 90	0.6
3	Eudragit EPO	10
4	Sodium Lauryl Sulphate	1.2
5	Talc	3.1
6	Mannitol SD 200	179.66
	Extragranular	
7	DH + Eudragit EPO	204.56
8	Mannitol SD 200	54.16
9	Cross Povidone XL 10	8.4
10	Sucralose	1.4
11	Colloidal Silicon Dioxide (Aerosil)	1.4
12	Magnesium Stearate	2.8
	Total weight in mg	280

Solution Preparation: Take 70% water, add Eudragit EPO to it and stir it. Add Stearic acid, SLS and Talc to it.

For Granulation: Weigh accurate quantity of drug, PVP K 90 and water. Granulate with planetary mixer. Pass the mass through 40 # and dry at 40 ºC for 30 min. LOD was checked.

TABLE 3: TASTE MASKING BY EUDRAGIT RL 30D.B. NO: 10-F002

S. no.	Ingredients	mg/tab
	Intragranular	
1	Donepezil Hydrochloride	10
2	Mannitol SD 200	152
3	Cross Povidone XL 10	14
4	Calcium Silicate	14
5	Eudragit RL 30 D	14.56
	Extragranular	
6	DH + Eudragit RL 30D	204.56
7	Mannitol SD 200	54.16
8	Calcium Silicate	8.4
9	Cross Povidone XL 10	8.4
10	Sucralose	1.4
11	Colloidal Silicon Dioxide (Aerosil)	1.4
12	Magnesium Stearate	2.8
	Total weight in mg	280

Procedure: All ingredients were weighed accurately, Intragranular part with DH was granulated by adding 20 % of the above solution. Remaining 80 % solution was top sprayed in GPCG. The extragranular part was blended with the intragranular part for 10 min and lubricated with magnesium stearate for 5 min.

TABLE 4: TASTE MASKING BY PUROLITE C 115 HMR. STIRRING TIME: 3 HRS

S. no.	Ingredients	Batch No.		
		10-F003 mg/ Tab.	10-F004 mg/ Tab.	10-F005 mg/ Tab.
	Intragranular			
1	Donepezil Hydrochloride	10	10	10
2	HMR	10	20	30
3	Water	q.s	q.s	q.s
	Extragranular			
4	Colloidal Silicon Dioxide (Aerosil)	1.4	1.4	1.4
5	Cross Povidone XL 10	22.4	22.4	22.4
6	Mannitol SD 200	231.85	221.85	211.85
7	Sucralose	1.4	1.4	1.4
8	Ferric Oxide Red	0.15	0.15	0.15
9	Magnesium Stearate	2.3	2.3	3.75
	Total weight in mg	280	280	280

Procedure: Weigh all ingredients, after activation of resin, a given amount of DH and Resin was stirred for 3 h. this complex was dried in hot air oven.

Lubricate this with magnesium stearate for 5 min. The disintegration time was noted.

Taste Masking of Donepezil HCL by Purolite C 115 KMR Polacrilin Potassium: DH was placed in a beaker containing 30 ml of deionized water and allowed to swell for 30 min. The pH of the resin solution was adjusted to 7 by using 1 M KOH. Accurately weighed DH was added and stirred for 3 h. The mixture was filtered and the

residue was washed with three portions of 75 ml of deionized water and dried. A bound drug in the complex was calculated as drug-loading efficiency. 6 gm of resin was soaked for 30 min with stirring at 400 rpm in 90 ml of deionized water. 3 gm of the drug was added to resin dispersion after adjusting pH 7. Nine samples were withdrawn at intervals of 30 min up to 4 h and were analyzed for drug loading efficiency at 231 nm [16].

TABLE 5: FORMULATION OF ORODISPERSIBLE TABLETS STIRRING TIME 30 H

S. no.	Ingredients	Batch No.			
		10-F006	10-F007	10-F008	10-F009
	Intragranular				
1	Donepezil Hydrochloride	10	10	10	10
2	Polacrilin Potassium	10	20	30	30
3	Water	q.s	q.s	q.s	q.s
	Extragranular				
4	Colloidal Silicon Dioxide (Aerosil)	1.4	1.4	1.4	1.4
5	Cross Povidone XL 10	22.4	22.4	22.4	22.4
6	Mannitol SD 200	231.85	221.85	211.85	211.85
7	Sucralose	1.4	1.4	1.4	1.4
8	Ferric Oxide Red	0.15	0.15	0.15	0.15
9	Magnesium Stearate	2.3	2.3	3.75	3.75
	Total weight in mg	280	280	280	280

Procedure: Weigh all ingredients; after activation of resin, the given amount of Donepezil HCL and resin was stirred for 3 h. This complex was dried in hot air oven with this drug resin complex extra granular part blended for 10 min. Lubricate this with magnesium stearate.

Ultra Violet spectroscopy of Donepezil HCl: When examined in the range 200 nm to 400 nm, a 0.001 percent w/v solution in methanol shows an absorption maximum at about 230 nm, 268 nm and 313 nm.

Evaluation Parameters:

Bulk Density: Weigh accurately 20 gm of blend pass through 18 # sieve, Transfer in dry 100 ml graduated cylinder. Calculate the appearance bulk density in g/ml by the following formula [18]:

Bulk density = Weight of the powder / Volume of the packing = W/ V0

Tapped Density: Weigh accurately 20 gm of blend pass through 18 # sieve to break up agglomerate Tap the cylinder for 500 times initially and measure the tapped volume (V1) to the nearest graduated units, repeat the tapping for additional 750 times and measure the tapped volume (V2) to the nearest graduated units. If the difference between the two volumes is less than 2 % then volume (V2) is taken as final tapped volume. If the difference is not less than 2 % then repeat tapping in increment of 1250 tap.

Tapped density = Weight of the powder / Tapped volume of the packing

Powder Compressibility:

Hausner's Ratio: It is the ratio of tapped density to the apparent density. Hausner's Ratio was calculated as:

Hausner's Ratio = Tapped density/ Bulk density

Compressibility Index: The packing ability of the drug was evaluated from a change in volume. It is indicated as Carr's compressibility index (CI) and can be calculated as follows:

C.I. % = Tapped density - Bulk density × 100 / Bulk density

Flow Property: A flow property depends on particle size, shape, porosity, and bulk density of powder. Angle of repose is defined as the maximum angle that can be obtained between the freestanding surface of a powder heap and the horizontal plane.

$$\tan \theta = h/r$$

Where, h = Height of pile, r = Radius of the base of pile, θ = Angle of repose.

Evaluation of Tablets:

Physical Parameter: The tablets were compressed using 9.4 mm diameter, flat-shaped punches on a Cad mach multi station rotary tablet machine. The tablet weight was kept at 280 mg and hardness between 5-7 kg/cm^2. Other parameters like size,

thickness, shape, hardness, friability, weight variation, wetting time were carried out.

***In-vitro* Disintegration Test:** Wire Basket Type Disintegration Apparatus: *In-vitro* disintegration apparatus consisted of a glass beaker of 1000 ml capacity the beaker contained 900 ml of disintegrating medium, the basket had only 6 ml of it. A magnetic bead was placed at the bottom of the beaker maintained at 37 ± 2 ºC.

Taste Evaluation: Volunteers in the age group of 20 to 25 years performed taste evaluation of DRC. The study protocol was explained and written consent was obtained from volunteers. DRC equivalent to 10 mg donepezil hydrochloride was held in the mouth for 15 seconds by each volunteer, and the bitterness level was recorded [17].

Weight Variation: Weighed 20 tablet sp individually, calculated the average weight, and compared the individual tablet weights to the average. The tablets meet the test if not more than two tablets are outside the percentage limit and none of the tablet differs by more than two times the percentage limit. The weight variation tolerance for uncoated tablets differs depending on average weight of the tablets.

Chemical Parameters:

Assay: Determined by liquid chromatography09: Test solution. Transfer intact tablets, add mobile phase and sonicate again for 30 minutes, and cool and make up the volume with mobile phase. Allow the excipients to settle down completely and dilute finally with mobile phase to obtain a solution of the final concentration of 0.01 percent w/v and filter.

Reference Solution: Transfer an accurately weighed quantity of about 55 mg of donepezil hydrochloride reference standard to a 50 ml volumetric flask. Dissolve and dilute to volume with methanol: 0.1 mol/L hydrochloric acid solution (3:1) and mix. Dilute 5.0 mL of this solution to 50.0 mL with dissolution medium and mix. Further, dilute 3.0 mL of this solution to 100.0 mL with dissolution medium and mix. Inject the reference solution. The test is not valid unless the column efficiency is not less than 7000 theoretical plates.

Dissolution:

***In-vitro* Dissolution Studies:** The *in-vitro* dissolution study of the prepared formulations was carried out in USP dissolution test apparatus type 2 (paddle). Release was compared with that of the marketed tablet. Dissolution medium 900 ml of (0.1 N HCL), temperature37 ± 0.5° C, 50 RPM, Volume withdrawn was 5 ml after 5 min.

RESULT:

Preformulation Study:

Loss on Drying: The quantity of moisture present in Donepezil HCl is 0.98%.

Melting Point: The melting point is about 211 ºC-212 ºC. λ_{max} for API was found to be 231 nm is shown in the figure.

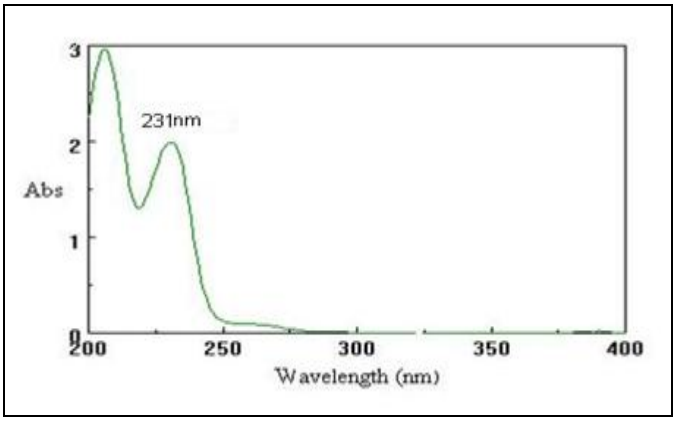

FIG. 1: UV SPECTROSCOPY FOR DONEPEZIL HCL

Drug Excipient Compatability Study: The results are illustrated in following **Table 6** given as follows:

TABLE 6: DETERMINATION OF PHYSICAL APPEARANCE FOR DRUG EXCIPIENT COMPATIBILITY STUDY

Sr. No.	Drug-Excipients combination	D:E Ratio	Observation			
			Initial		1 Month 40 °C/75%RH	
			Colour	Lumps	Colour	Lumps
M1	API	-	+	+	+	+
M2	API + Mannitol SD 200	1:1	+	+	+	+
M3	API + Polacrilin Potassium	1:1	+	+	+	+
*M4	API + Cross Povidone XL 10	1:1	+	+	+	+
M5	API + Aerosil	1:1	+	+	+	+
M6	API+ Magnesium Stearate	1:1	+	+	+	+

M7	API+ Sucralose NF	1:1	+	+	+	+
M8	API+ Eudragit EPO	1:1	+	+	+	+
M9	API+ Eudragit RL 30D	1:1	+	+	+	+
M10	API+ HMR	1:1	+	+	+	+
M11	API+ Calcium Silicate	1:1	+	+	+	+

+ =No colour Change and lumps free.

XRD: The results are illustrated in following **Fig. 2**, **3**, **4** as follows:

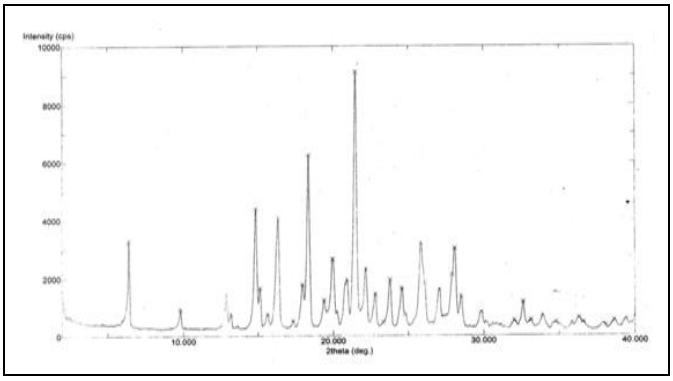

FIG. 2: XRD PATTERN OF DONEPEZIL HCL

Observation: Fig. 2 Show sharp intense and characteristic peaks of Donepezil HCl was found to be highly crystalline nature.

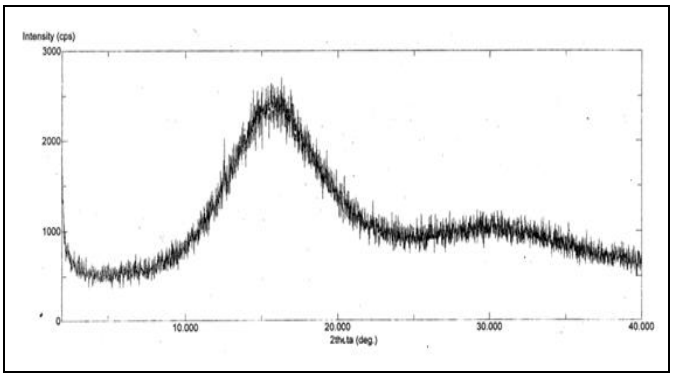

FIG. 3: XRD FOR AMORPHOUS FORM OF DONEPEZIL HCL

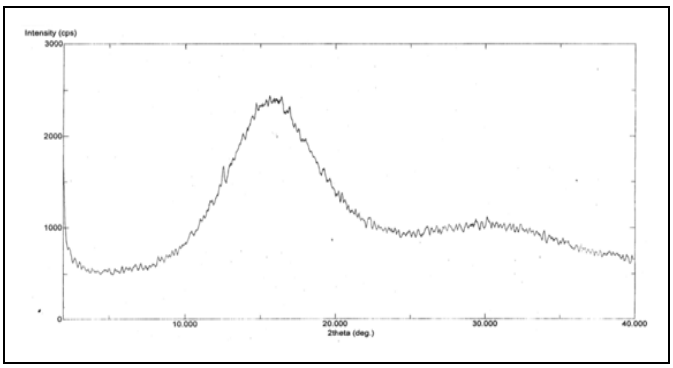

FIG. 4: XRD AMORPHOUS FORM OF DONEPEZIL HCL (SMOOTHING)

Fig. 3 and **4** show less intense and different peaks. X-ray diffraction patterns of drug resin complexes were found to be diffused, confirming that a new amorphous solid phase had been obtained.

Drug Excipient Interaction by FTIR: The results are illustrated in following **Fig. 5**, **6**. FTIR for Donepezil HCL API is shown in **Fig. 5** as follows:

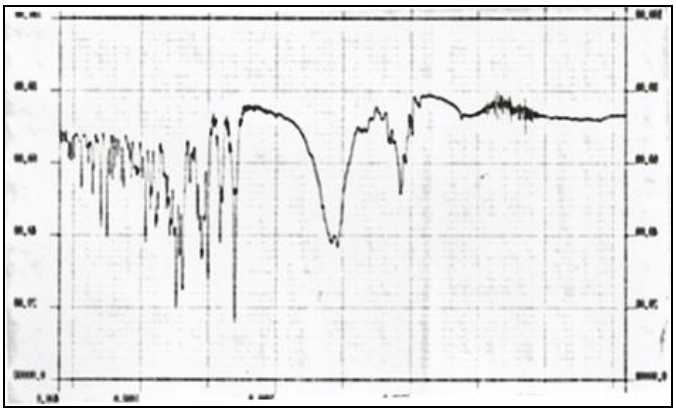

FIG. 5: FTIR FOR DONEPEZIL HCL

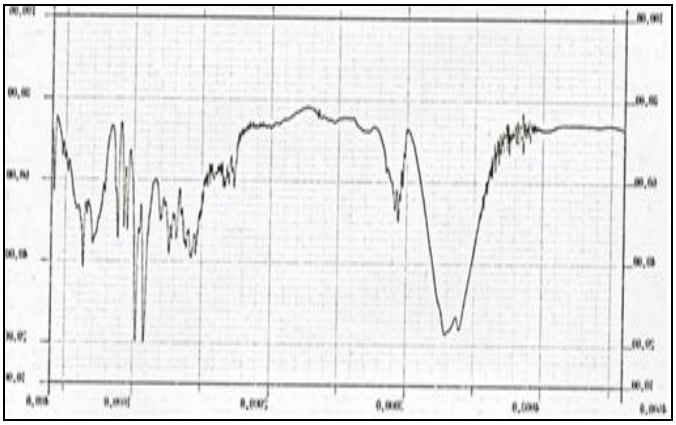

FIG. 6: FTIR FOR DRUG+ EXCIPIENTS

Formulation of Orodispersible Tablets: As per Tab.no.02 Taste masking by Eudragit EPO, Batch No. 10-F001. The disintegration time of the tablet was found to be more than 2 min 40 sec. Also, the taste of the tablet was found to be metallic. Hence strategy changed to Eudragit RL 30D, as per Tab. 04 It was found that taste was not properly masked. Hence strategy changed to Potassium Polacrilin as per **Table 5.**

Various parameters affecting taste masking like a drug: resin ratio and stirring time were optimized

with efficient loading of DH. The volunteers rated the complexes as tasteless and agreeable. Drug release from DRC in salivary pH was insufficient to impart bitter taste. Complete drug release was observed at gastric pH. Standard Calibration Curve is shown in **Fig. 7** as follows.

Standard Calibration Curve:

TABLE 8: ABSORBANCE FOR STANDARD CALIBRATION CURVE

Sr. No.	Concentration (ug/ml)	Absorbance
1	0	0
2	2	0.138
3	4	0.236
4	6	0.347
5	8	0.454
6	10	0.577
7	12	0.673

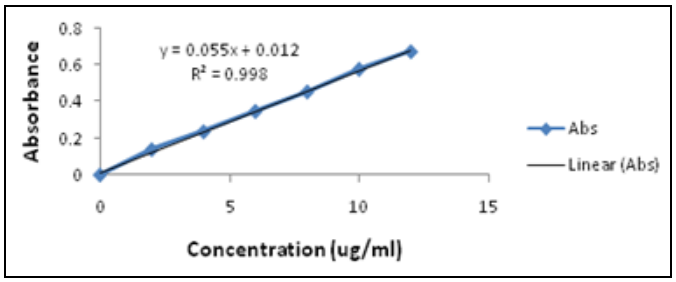

FIG. 7: STANDARD CALIBRATION CURVE FOR DONEPEZIL HCL IN 0.1N HCL

TABLE 7: FT-IR STUDY OF DONEPEZIL HYDRO-CHLORIDE AND PHYSICAL MIXTURE OF DRUG AND EXCIPIENTS

S. no	Material(s)	Functional group(s)	FT-IR signaling(cm^{-1})	
			Standard	Observed
1	Donepezil HCL	N-H	1350-1000	3044.0
		C=O	1740-1680	1697.6
		C=C	1660-1600	1589.5
2	Tablet powder	N-H	1350-1000	3289.0
		C=O	1740-1680	1736.1
		C=C	1660-1600	1560.6

The FT-IR study revealed that there were no interactions taking place between Donepezil HCL and excipients. Donepezil HCL and excipients were found to be compatible with each other.

Content Uniformity: The results are illustrated as follows; Donepezil Tablets contain not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of donepezil hydrochloride, $C_{24}H_{29}NO_3$, HCl.

The assay of Marketed sample was found to be in specified limit for specified stability period. This test Complies with IP limits.

Bulk Density and Tapped Density: The results are illustrated as follows in **Table 11.**

TABLE 9: DETERMINATION OF CONTENT UNIFORMITY OF MARKETED FORMULATION

Parameter	Stability Condition						
	Initial	1 Month		2 Months		3 Months	
		25^0C/ 60%RH	40^0C/ 75%RH	25^0C/ 60%RH	40^0C/ 75%RH	25^0C/ 60%RH	40^0C/ 75%RH
Assay (%w/v)	99.1	97.3	96.9	94.4	93.7	92.0	91.2

Dissolution Study:

TABLE 10: DISSOLUTION STUDY PROFILE FOR MARKETED FORMULATION

Dissolution Study Time (Sec.)	Stability Condition / % Drug Release						
	Initial	1 Month		2 Months		3 Months	
		25^0C/ 60%RH	40^0C/ 75%RH	25^0C/ 60%RH	40^0C/ 75%RH	25^0C/ 60%RH	40^0C/ 75%RH
0	0	0	0	0	0	0	0
5	55.6	55.1	55.0	54.2	53.6	52.8	52.0
10	75.9	75.2	74.6	74.1	73.9	73.4	73.0
15	79.8	79.2	78.5	78.1	77.6	77.2	76.2
20	85.2	85.0	84.2	83.8	83	82.9	82.2
30	92.4	91.8	91.2	90.6	90.1	89.6	89.1
45	95.4	95.1	94.78	93.2	92.9	92.8	92.6

TABLE 11: DETERMINATION OF BULK AND TAPPED DENSITY OF FORMULATED TABLET BATCHES

S. no	Batch No.	Bulk Density* (g/cc)	Tapped Density* (g/cc)
1	10-F001	0.55	0.73
2	10-F002	0.59	0.79
3	10-F003	0.58	0.78

4	10-F004	0.53	0.7
5	10-F005	0.57	0.71
6	10-F006	0.52	0.67
7	10-F007	0.54	0.69
8	10-F008	0.58	0.69
9	10-F009	0.54	0.66

*Average of three observation, Mean +SD

Flow Property:

TABLE 12: DETERMINATION OF FLOW PROPERTY OF FORMULATED TABLET BATCHES

S. no	Batch No.	Compressibility Index	Haunsner's Ratio	Angle of Repose(^{0})	Flow property
1	10-F001	23.60	1.32	29^0 12'	Excellent
2	10-F002	25.22	1.34	30^0 56'	Good
3	10-F003	23.61	1.34	32^0 70'	Good
4	10-F004	20.00	1.32	30^0 33'	Excellent
5	10-F005	19.42	1.25	29^0 81'	Excellent
6	10-F006	21.57	1.29	32^0 76'	Good
7	10-F007	20.38	1.28	35^0 64'	Fair
8	10-F008	18.93	1.19	28^0 91'	Excellent
9	10-F009	21.32	1.22	29^0 03'	Excellent

*Average of three observation, Mean +SD

TABLE 13: REPRESENTING THE OPINION OF VOLUNTEERS

Sr. no.	Taste masking agents	Batch No.	Opinion*
1	API+Eudragit EPO(1:1)	10-F001	5
2	API+Eudragit RL30D(1:1)	10-F002	5
3	API+HMR(1:1)	10-F003	6
4	API+HMR(1:2)	10-F004	7
5	API+HMR(1:3)	10-F005	7
6	API+KMR(1:1)	10-F006	6
7	API+KMR(1:2)	10-F007	7
8	API+KMR(1:3)	10-F008	8
9	API+KMR(1:3)	10-F009	8

*Average of three observation

Taste Evaluation: The taste of theresinate was checked by 20 healthy volunteers. Sample equivalent to normal dose was held in the mouth for 10 seconds & volunteers were asked to evaluate taste of intragranular part made by different taste making agents. This test evaluates the acceptability of taste-masking agents. Bitterness values are based on 1-10 scale with 1 being strong bitter to 10 being excellent.

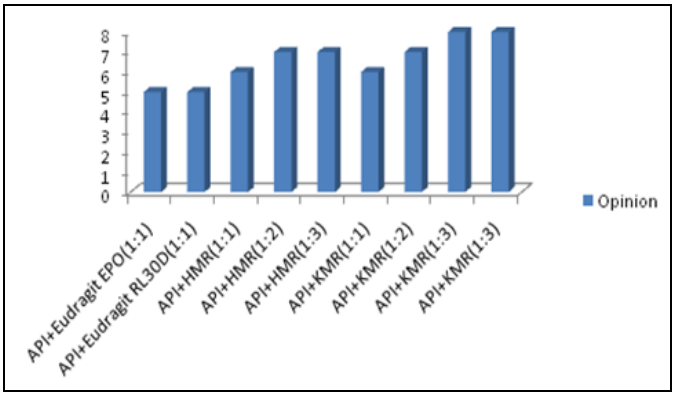

FIG. 8: BAR DIAGRAM REPRESENTING THE OPINION OF VOLUNTEERS

LOD: It was determined as per the procedure given in the material and method part. The results are illustrated in **Table 14** as below;

TABLE 14: DETERMINATION OF LOD OF FINAL BLEND OF FORMULATION BATCHES

Parameter	Batch No.								
	T1	T2	T3	T4	T5	T6	T7	T8	T9
LOD (%)	2.25	2.15	1.99	2.13	2.45	1.92	1.97	2.06	1.98

Post Compression Parameter:

Physical Evaluation: Determination of hardness, thickness, friability and weight variation of formulated tablet batches is shown in table 15 as follows;

TABLE 15: DETERMINATION OF HARDNESS, THICKNESS, FRIABILITY AND WEIGHT VARIATION OF FORMULATED TABLET BATCHES

Sr. No.	Batch No.	Thickness (mm)	Hardness (Kpa)	Friability (%)	Wt. Variation*
1	10-F001	4.0	5.1	0.2	0.537558 +0.3288
2	10-F002	3.9	5.2	0.3	0.537696 +0.328921

3	10-F003	4.1	5.3	0.2	0.537742 +0.328995
4	10-F004	3.9	6.1	0.1	0.537558 +0.328702
5	10-F005	3.9	4.9	0.2	0.537622 +0.328804
6	10-F006	4.1	5.0	0.3	0.537558 +0.328702
7	10-F007	4.0	5.5	0.3	0.521648 +0.310698
8	10-F008	4.1	5.3	0.2	0.537696 +0.328921
9	10-F009	3.9	5.2	0.2	0.537696 +0.32892

*Average of three observation, Mean +SD.

Determination of Disintegration Time and Wetting time of formulated tablet batches is shown in **Table 16** as follows;

TABLE 16: DETERMINATION OF DISINTEGRATION TIME AND WETTING TIME OF FORMULATED TABLET BATCHES

S. No.	Batch No.	Disintegration Time*(Sec)	Wetting Time*(Sec)
1	10-F001	18	25
2	10-F002	19	24
3	10-F003	16	27
4	10-F004	15	25
5	10-F005	16	28
6	10-F006	17	26
7	10-F007	16	25
8	10-F008	15	24
9	10-F009	15	24

*Average of three observation

Chemical Evaluation: Content Uniformity: Determination of Content Uniformity of formulated tablet batches is shown in **Table 17** as follows;

TABLE 17: DETERMINATION OF CONTENT UNIFORMITY OF FORMULATED TABLET BATCHES

Sr. No.	Batch No.	Assay*(%w/v)
1	10-F001	97.2
2	10-F002	97.1
3	10-F003	97.2
4	10-F004	96.7
5	10-F005	96.4
6	10-F006	96
7	10-F007	95.2
8	10-F008	98.7
9	10-F009	99.6

*Average of three observation.

Dissolution Study: Comparative study of % drug release of Batch 10-F001, 10-F002, 10-F003, 10-F004 and 10-F005 is shown in **Fig. 9** as follows:

TABLE 18: DETERMINATION OF % DRUG RELEASE OF FORMULATED TABLET BATCHES

Dissolution Study Time (Min.)	Batch No. / % Drug Release								
	10-F001	10-F002	10-F003	10-F004	10-F005	10-F006	10-F007	10-F008	10-F009
0	0	0	0	0	0	0	0	0	0
5	71.59	80.4	60.58	57.35	59.45	73.05	74.18	82.44	89.72
10	82.11	87.13	72.56	64.31	64.31	74.02	80.49	89.4	95.06
15	85.35	92.96	77.26	72.56	67.38	78.87	82.44	95.06	96.68
20	88.59	93.6	80.49	73.05	73.05	80.49	89.88	97.17	97.17
30	91.82	93.6	80.82	80.49	75.96	91.99	91.99	101.37	99.92
45	95.06	93.77	80.82	80.49	80.82	91.99	92.75	101.54	100.24

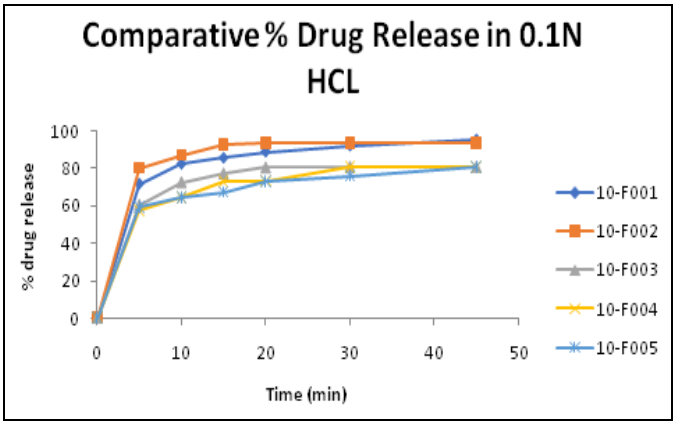

FIG. 9: COMPARATIVE STUDY OF % DRUG RELEASE OF BATCH 10-F001, 10-F002, 10-F003, 10-F004 AND 10-F005

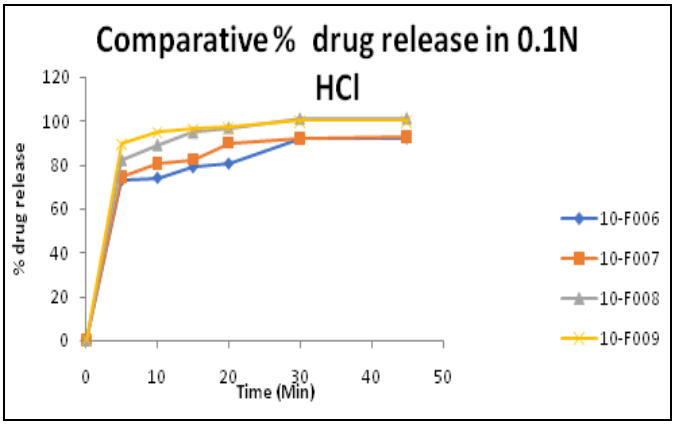

FIG. 10: COMPARATIVE STUDY OF % DRUG RELEASE OF BATCH 10-F006, 10-F007, 10-F008 AND 10-F009

Comparative study of % drug release of Batch 10-F006, 10-F007, 10-F008 and 10-F009.Comparative study of % drug release of Batch 10-F006, 10-F007, 10-F008 and 10-F009 is shown in **Fig. 10** as follows: The results are illustrated as follows: Determination of % Drug Release of Optimized Reproduced batch is shown in **Table 19** as follows;

TABLE 19: DETERMINATION OF % DRUG RELEASE OF OPTIMIZED REPRODUCED BATCH

Dissolution Study Time (Min.)	Stability Condition / % Drug Release						
	Initial	1 Month		2 Months		3 Months	
		25^0C/60% RH	40^0C/75%RH	25^0C/60%RH	40^0C/75%RH	25^0C/60%RH	40^0C/75%RH
0	0	0	0	0	0	0	0
5	2.44	82.40	82.0	81.85	81.5	80.8	80.6
10	89.4	89.4	89.1	88.5	88.1	87.8	87.5
15	.06	95.0	94.4	94.3	94.1	93.7	93.4
20	97.17	97.0	96.5	96.1	95.8	95.5	95.1
30	101.37	99.98	99.8	99.6	99.4	98.0	97.8
45	01.54	100.1	99.9	99.8	99.7	98.2	98.1

Comparative study of % drug release of Marketed tablet & Batch 10-F009.Comparative study of % drug release of Marketed and 10-F009 is shown in **Fig. 11** as follows;

TABLE 20: COMPARATIVE STUDY OF % DRUG RELEASE OF MARKETED TABLET & BATCH 10-F009

Time (Min.)	Marketed	10-F009
0	0	0
5	55.6	89.72
10	75.9	95.06
15	79.8	96.68
20	85.2	97.17
30	92.4	99.92
45	94.1	100.24

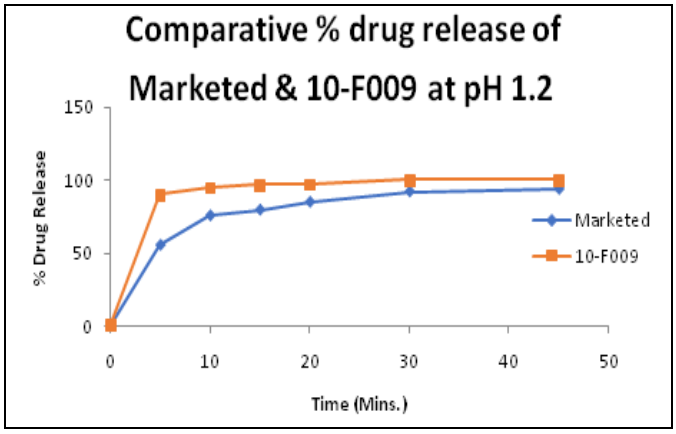

FIG. 11: COMPARATIVE STUDY OF % DRUG RELEASE OF MARKETED AND 10-F009

DISCUSSION: Donepezil HCL was extremely bitter in taste. The objective was to develop generic donepezil oral dispersible tablet and compare it with marketed formulation. X-Ray diffractogram of Donepezil HCL confirms its crystalline nature, as evidenced from the number of sharp and intense peaks **Fig. 2**. The diffraction pattern of polymer (Potassium Polacrilin) + Donepezil HCL complex showed complete disappearance of crystalline peaks of drug **Fig. 3**. These findings suggest the formation of a new solid phase with a lower degree of crystallinity due to complexation **Fig. 4** [14]. **Fig. 5** and **6** shows the FT-IR spectra of Donepezil HCl and optimized blend of Donepezil HCl oral formulation. Their overall patterns in the fingerprint region were similar. The most intensive absorption band around 1697 cm^{-1} in the spectra is attributed to the stretching vibrations of C=O group in the structure of DH. Absorption bands around 1589.5 cm^{-1} are contributed by C=C aliphatic groups. Donepezil HCl was found to be soluble in organic solvents such as methanol. A simple, reproducible method of estimation was carried out in methanol ranging from 5-40 mcg/ml solutions at 231 nm against the blank. The standard graph obtained was linear, with a regression coefficient 0.998.

Donepezil HCl oro dispersible tablet was formulated. **Table 2, 3, 4, 5** was formulated by using different taste-masking agents *e.g.*, Eudragit EPO, Eudragit RL 30 D , Purolite C115 HMR and Purolite C11 5 KMR in the ratio of 1%, 2% and 3% as represented by 10-F001 to 10-F009 respectively. These formulations were evaluated for the pre-compression and post-compression parameters [14, 15]. Tapped density of the formulations was in between 0.66-0.79 gm/ml, whereas the bulk density, was in the range of 0.52-0.59 gm/ml. The compressibility values varied from 18.93% - 25.22%. The angle of repose values of the

formulations varied from 28˚to 35˚. From these values, it was evident that these blends had good flow properties.18 Physical parameters was found within the specification of I.P 2007. The average weight of all the 9 formulation were found in the range of 280 mg. The thickness of the all the formulations was found to be in the range of 4.0-4.1 mm. The hardness of the 10-F001 to 10-F009 formulation was found to be 5.0 Kg/cm^2 to 7.0 Kg/cm^2 9. Friability of the 10-F001 to 10-F009 was found to be 0.1 to 0.3. The wetting time of the formulation 10-F001 and 10-F002 was found to be 25 & 24 sec. Also wetting time of 10-F003, 10-F004, 10-F005 was found to be 27, 25 & 28 sec, respectively.

Wetting time of 10-F006, 10-F007, 10-F008 and reproducible batch 10-F009 was found to be 26, 25, 24 and 24 sec respectively [17]. Drug content of the 10-F001, 10-F002 was found to be 97.2, 97.1 w/v respectively where as 10-F003,10- F004 and 10-F005 was 97.2, 96.7 and 96.4% w/v respectively. 10-F006, 10-F007, 10 –F008 and 10- F009 was 96, 95.2, 98.7 and 99.6% w/v respectively. The disintegration time of different formulations is given in the table and found to be less than 17 seconds.

The disintegration time of the reproducible (10-F009) batch was found to be 15 sec. The disintegration time of the marketed tablet of Donepezil HCl was found to be 17 sec which is higher than 10-F009 tablets [17, 18]. In vitro dissolution of various formulations at different time intervals is shown from **Fig. 14** & **15**. Optimized formulation released drug at a greater rate than that of the innovator **Fig. 16**.

Formulation with 1:3 API+ KMR ratio (Batch No. 10-F009) shows 100 %in 0.1 N HCL drug release at 45 min. The *in-vitro* dissolution of the marketed tablet was found to be 94.1 % in 0.1N HCL [9, 18]. The release of 10-F001 was found to be 95.06 %, while that of 10-F002 was found to be 93.77% but taste was not properly masked. Metallic taste of Eudragit appears in the formulation. Thus, the approach was changed to HMR. The release of 10-F003, 10-F004, 10-F005 was found to 80.82, 80.49 and 80.82% but taste was not properly masked. Thus, strategy changed to KMR. The release of 10-F006, 10-F007, 10-F008 was found to be 91.99, 92.75 and 101.54. Also, the bitter taste of donepezil hydrochloride was properly masked. Dissolution of 10-F009, reproducible batch of 10-F008 matched with the dissolution of the marketed tablet. Based on the data obtained from the stability study, it was concluded that the batch 10-F009 formulation would maintain stability and potency throughout the study period.

ACKNOWLEDGEMENT: The author would like to thanks the Principal and guide to provide technical support and to give resolved guidance.

CONFLICT OF INTEREST: All authors have no conflict of interest.

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How to cite this article:
Patel MJAJ, Rathod SB and Mankar SS: Taste masking, design and evaluation of oral dispersible tablet of anticholinesterase agent. Int J Pharm Sci & Res 2021; 12(12): 6540-52. doi: 10.13040/IJPSR.0975-8232.12(12).6540-52.