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DESIGN AND EVALUATION OF ORAL FAST DISSOLVING THIN STRIPS LOADED WITH DONEPEZIL HYDROCHLORIDE

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ABSTRACT: The aim of present study deals with the Design and evaluation of oral fast dissolving thin strips loaded with Donepezil hydrochloride. Donepezil HCl is a specific noncompetitive reversible inhibitor of acetyl cholinesterase (AChE) used in the treatment of Alzhiemer's disease. Films were formulated using film forming polymer like Sodium alginate, Pectin, Polyvinyl alcohol by Solvent casting technique. The films were evaluated for weight variation, thickness, surface pH, folding endurance, drug content, disintegration time, moisture content, moisture uptake, tensile strength, vapour transmission rate, in-vitro dissolution studies by pharmaceutical standard methods. Based on the evaluation parameters optimized strips were formulated. The optimized strips were kept for accelerated stability studies as per ICH guidelines (Zone IV) at 45C & 75% relative humidity. It was found that there was not any substantial interactions between drug content and the prepared formulations were stable. Among the formulations FV1 and FC2 were found to be best based on evaluation parameters and stability studies. After performing stability study it was observed that at accelerated conditions 40˚ ± 2˚C and 75 % ± 5 % RH there was no change in % drug content of the formulation FV1 and FC2. At zero day the drug content for formulation FV1 and FC2 was found to be 97.5±0.25 and 98±0.02 respectively and after 1 month it was95.8±0.23 % and 96.9±0.03 %.for formulation FV1 and FC2 respectively.

KEY WORDS Oral fast dissolving strips, Donepezil HCl, Alzheimer's

1. Introduction

1.1 Oral medicated strip/ film

A strip or film can be defined as a dosage form that employs a water dissolving polymer (generally hydrocolloid, which may be a bio adhesive polymer), which allows the dosage form to quickly hydrate, adhere

and dissolve when placed on the tongue or oral cavity (i.e. buccal, palatal, gingival, lingual or sublingual, etc.) to provide rapid local or systemic drug delivery.

1.1.1. Classification of oral film[1-2]:

There are three different subtypes:

(1) Flash release,

(2) Mucoadhesive melt-away wafer,

(3) Mucoadhesive sustained-release wafers.

Table 1: Types of oral films [1-2]

Sub Type/ Property	**Flash release wafer**	**Mucoadhesive melt-away wafer**	**Mucoadhesive sustained release wafer**
Area (cm2)	2-8	2-7	2-4
Thickness(µm)	20-70	50-500	50-250
Structure	Film: single layer	Single or multilayer System	Multi-layer system
Excipients	Soluble, highly hydrophilic polymers	Soluble, hydrophilic Polymers	Low/Non-soluble Polymers
Drug phase	Solid solution	Solid solution or suspended drug particles	Suspension and/or solid Solution
Application	Tongue (upper palate)	Gingival or buccal Region	Gingival, (other region in the oral cavity)
Dissolution	Maximum 60 seconds	Disintegration in a few minutes, forming gel	Maximum 8-10 Hours.

Table 2: OTC and prescription OTF examples used in the world [3]

Trade name	Year	Drug	Polymer	Plasticizer
OTC products				
Listerine, PocketPaks® oral care strips (Johnson & Johnson)	2001	Menthol	Pullulan	Glyceryl oleate Macrogol
Sudafed® PE (Johnson & Johnson)	2005	Phenylephrine	Maltodextrin Pullulan Carrageen	Glycerin
Theraflu® Day Time Thin Strips (Novartis Consumer Healthcare)	2004	Dextromethorphan Diphenhydramine Phenylephrine	Hypromellose (HPMC) Maltodextrin	Propylene Glycol Macrogol
Gas-X Thin Strips® (Novartis Consumer Healthcare)	2006	Simethicone	Maltodextrin HPMC	Polyethylene glycol Sorbitol
Chloraseptic® Sore Throat Relief Strips (InnoZen)	2004	Benzocaine	Corn starch	Erythritol Macrogol
Suppress Cough Strips® (InnoZen)	2005	Menthol	Carrageen Pectin Sodium alginate	Glycerin
Pedia-Lax™ Quick Dissolve Strip (C. B. Fleet)	2008	Sennoside	HPMC	Glycerin
SpotScent Oral Care Strips® (Spotscent)	2003	Parsley seed oil	Modified cellulose	Glycerin
Orajel™ Kids Sore Throat Relief Strips (Church & Dwight Co.)	2007	Benzocaine	Pectin	Glycerin
Day Time Triaminic Thin Strips® Cough & Cold (Novartis Consumer Healthcare)	2004	Phenylephrine Dextromethorphan	HPMC	Polyethylene glycol
IvyFilm®, IvyFilm Kiddies® Extract (Lamar-Forrester Pharma)	2016	Hedera Helix	Pullulan	Glycerin
Benadryl® Allergy Quick Dissolve Strips (McNeill-PPC)	2006	Diphenhydramine	Carrageen Pullulan	Glycerin
Prescribed products				
Sildenafil Sandoz Orodispersible Film® (Sandoz)	2014	Sildenafil	HHPMC	Glycerin
Sildenafil Orodispersible Film (IBSA Farmaceutici Italia Srl)	2016	Sildenafil	Maltodextrin	Glycerin polisorbat Propylene glycol Monocaprylate
Zuplenz® (Vestiq Pharmaceuticals)	2012	Ondansetron	HHPMC	Polyethylene oxide Colloidal silicon Dioxide
Risperidone HEXAL® SF Schmelzfilm	2010	Risperidone	HHPMC Maltodextrin	Glycerin

OTC: Over-the-counter, OTF: Oral thin film, HPMC: Hydroxypropyl methylcellulose

2. Material and methods

2.1. Preparation of fast dissolving strips

2.1.1. Solvent casting method:

1. The FDS of Donepezil was prepared by solvent casting method using polymers like sodium alginate, Pectin, PVA in different ratios.
2. The polymeric solution was prepared in double distilled water with constant stirring.
3. The polymeric solution was filtered through nylon gauze to remove debris and suspended particles.
4. The resultant solution was left overnight at room temperature to ensure a clear, bubble free solution.
5. The solution was poured into a petridish having a 7.5 cm diameter, 5mg/sqcm equivalent of donepezil was added to each strips.

6. Strips were dried in an oven at a temperature not exceeding 35ºC.
7. Dried strips were carefully removed from the petridish and evaluated.

Fig.1: Solvent casting method

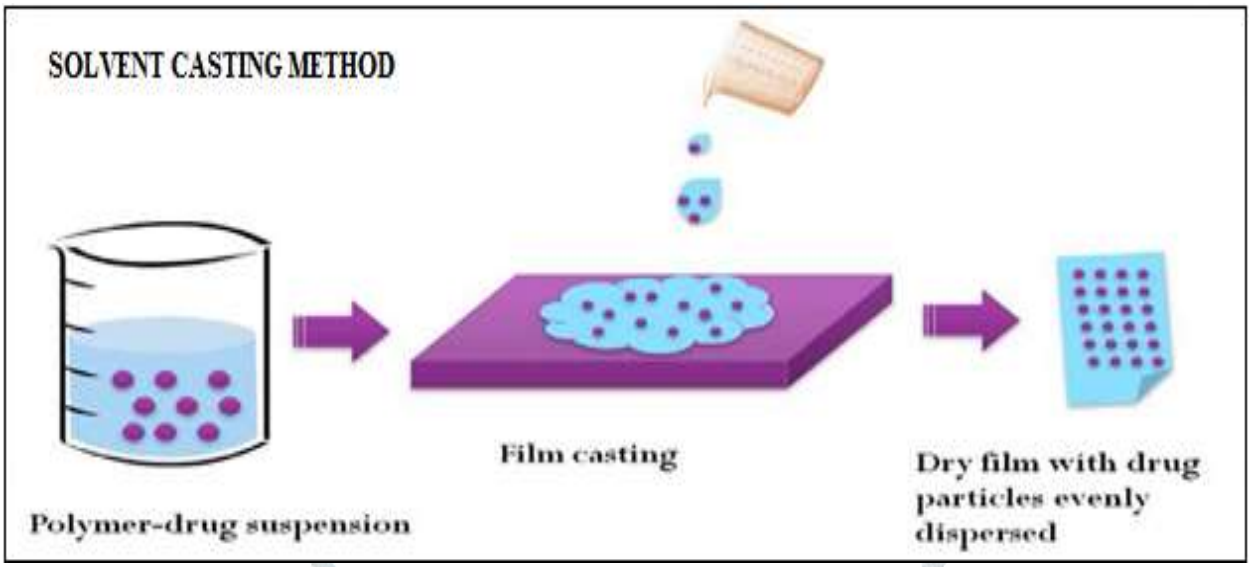


Table 2: Formulation table

Formulation	FS1	FS2	FS3	FS4	FP1	FP2	FP3	FP4	FV1	FV2	FV3	FV4	FC1	FC2
Drug(mg)	100	100	100	100	100	100	100	100	100	100	100	100	100	100
SA(mg)	300	400	450	500	-	-	-	-	-	-	-	-	50	-
Pectin(mg)	-	-	-	-	300	400	450	500	-	-	-	-	-	50
PVA(mg)	-	-	-	-	-	-	-	-	200	300	400	450	200	200
SSG(mg)	50	50	50	50	50	50	50	50	-	-	-	-	-	-
CCS(mg)	-	-	20	20	-	-	20	20	-	-	-	-	-	-
CP(mg)	-	-	-	-	-	-	-	-	50	50	50	50	50	50
Dextrose (mg)	100	100	100	100	100	100	100	100	200	200	200	200	200	200
CA(mg)	31	36	38.5	40	31	36	38.5	40	20	20	20	20	20	20
DW(ml)	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

SA- Sodium alginate, SSG- Sodium starch glycolate, CCS- CrossCarmellose Sodium, CP- Cross povidone, CA- Citric acid, PVA- Polyvinyl alcohol

2.2. Evaluation parameters:

2.2.1. Weight variation:

Weight variation is studies by individually weighing 10 randomly selected films and calculating the average weight. The average weight should not deviate significantly from the average weight.

2.2.2. Thickness [4]:

It can be measured by micrometer screw gauge or Vernier callipers. For content uniformity and uniform film thickness, it can be checked at five different points by calibrated digital micrometer.

2.2.3. Mechanical properties:

a) Tensile strength- It is point at which film is break [5]. Tensile strength of the films determined by using a tensile testing machine like Instron or Monsanto tester. It is calculated by the applied load at rupture divided by the cross sectional area of the strip as given in the equation below:

Tensile strength = Load at failure× 100÷ Film thickness× Film width

b) Percent elongation: On application of stress, a strip sample stretches and this is referred to as strain. Strain is basically the deformation of strip divided by original dimension of the sample. Generally, elongation of strip increases with increase in concentration of plasticizer [6].

It is calculated by the following formula:

% elongation= Increase in length×100/Original length

2.2.4. Folding endurance:

Folding endurance value is determined by the number of times the film is folded without breaking. It was determined by repeatedly folding one film at the same place till it brokes or folded up to 300 times manually, which was considered satisfactory to reveal good film properties. The number of times of film could be folded at the same place without breaking gave the value of the folding endurance. This test was done on randomnly selected three films for each [7].

2.2.5. Tear resistance:

Tear resistance value is the maximum force or stress required to tear the specimen [8-9]. It is expressed in Newton's or Pound-Force. Tear resistance of plastic film or sheeting is a complex function of its ultimate resistance to rupture. Basically very low rate of loading 51 mm (2 in.)/min is employed and is designed to measure the force to initiate tearing.

2.2.6. Surface pH of film:

The surface pH of fast dissolving strip was determined in order to investigate the possibility of any side effects in vivo. As an acidic or alkaline pH may cause irritation to the oral mucosa, it was determined to keep the surface pH as close to neutral as possible. A combined pH electrode was used for this purpose. Oral strip was slightly wet with the help of water. The pH was measured by bringing the electrode in contact with the surface of the oral film. The experiments were performed in triplicate, and average values were reported [10].

2.2.7. In vitro disintegration time:

Determined manually by dipping the film in 10 ml of water in beaker with gently shaking when film was dissolved, time was noted.

2.2.8. Contact angle:

It is measured by goniometer. In this method distilled water drop placed on dry film and picture is taken within 10 sec for angle determination [10].

2.2.9. In vitro dissolution test:

It is performed in USP type 2 apparatus in 0.1N HCl and 6.8 phosphate buffer. The samples withdrawn at various time intervals and analysed spectrophotometrically [11].

2.2.10. Drug content:

A film of size 2 cm^2 was cut and put 10 ml of volumetric flask which containing solvent. This was then shaken in a mechanical shaker for 2 hrs to get a homogeneous solution and filtered. The drug was determined spectroscopically by appropriate dilution.

2.2.11. Transparency:

It is determined using a simple UV spectrophotometer [12].In these film samples are cut into rectangles and kept on internal side of spectrophotometer cell.

2.2.12. Taste evaluation:

It is going with panel of volunteers and the test sensors analyzed the sweetness level of taste masking agents.

2.2.13. Packaging:

The most commonly used packaging format is aluminium pouch. Rapid card is used for packaging of Rapid films which is patented and proprietary packaging system of APR-Labtech [12-13].

2.2.14. Morphology study:

The morphology of the films is studies using electron microscopic (SEM), at definite magnification [14].

2.2.15. Moisture content:

Previously weighed films are stored in desiccators for 24 hours. The final weight is noted when there is no further change in the weight of individual film [15]. Percent of moisture content is calculated as follows:

$$\textit{Moisture content} = \frac{initial\ weight - final\ weight}{initial\ weight} \times 100$$

2.2.16. Moisture uptake:

This test is done by keeping previously weighed films in a dessicator at a particular temperature and relative humidity. After three days films is taken out and reweigh to determine the percent of moisture uptake. Percent of moisture uptake is calculated as follows [15]:

$$\textit{Moisture uptake} = \frac{Final\ weight - Initial\ weight}{initial\ weight} \times 100$$

2.2.17. Young's Modulus:

Young's modulus or elastic modulus is the measure of stiffness of film. It is represented as the ratio of applied stress over strain in the region of elastic deformation as follows:

$$Young's\ Modulus = \frac{Slope \times 100}{Film\ thickness \times Cross\ head\ Speed}$$

2.2.18. Swelling Percentage study:

Swelling study of prepared film was calculated by function of weight and area increases due to swelling which was measured for each formulation as follows. Weight increases due to swelling. A film of size (2x2 cm^2) diameter from every batch was weighed on a preweigh coverslip. It was kept in a petridish and 10ml of phosphate buffer pH 6.8 was added. After one hour the cover slip was removed and weighed. The differences in the weights gives the weight increase due to absorption of water and swelling of film[14] the study was conducted for 14 hrs. The percentage swelling ratio was calculated from average of three measurements using the following equation.

$$\%\ swelling\ ratio = \frac{Xt - Xo}{Xo} \times 100$$

Where Xt = weight or area of swollen film after time t.

Xo = weight of original film at time zero.

2.2.19. Vapour transmission test:

Vapour transmission method was employed for the determination of vapour transmission from the film. Glass bottle filled with 2g anhydrous calcium chloride and an adhesive (feviquick) spread across its rim, were used in the study. The film was fixed over the adhesive and the assembly was fixed in a constant humidity chamber, prepared using saturated solution of ammonium chloride and maintained at 37±2°C. The difference in the weight after 24hrs was calculated [16]. The experiments were carried out in triplicate and vapour transmission rate was calculated as follows:

VTR = (Amount of vapour transmitted)/ (Area×time)

3. Result & Discussion

Films were evaluated for weight variation, thickness, surface pH, folding endurance, drug content, disintegration time, moisture content, moisture uptake, tensile strength, vapor transmission rate, in-vitro dissolution studies by pharmaceutical standard methods. Based on the evaluation parameters optimized strips were formulated. The optimized strips were kept for accelerated stability studies as per ICH guidelines (Zone IV) at 45C & 75% relative humidity. It was found that there was not any substantial interactions between drug content and the prepared formulations were stable. Among the formulations FV1 and FC2 were found to be best based on evaluation parameters and stability studies. After performing stability study it was observed that at accelerated

conditions 40˚ ± 2˚C and 75 % ± 5 % RH there was no change in % drug content of the formulation FV1 and FC2. At zero day the drug content for formulation FV1 and FC2 was found to be 97.5±0.25 and 98±0.02 respectively and after 1 month it was95.8±0.23 % and 96.9±0.03 %.for formulation FV1 and FC2 respectively.

Table 2: Physicochemical parameters of prepared strips

Formulation Code	Thickness ±SD (mm)	Weight uniformity ±SD	Folding endurance ±SD	Surface Ph ±SD	*In vitro* DT
FS1	0.03±0.025	31.1±7.1	348±4.16	6.58±0.15	6.56min
FS2	0.14±0.020	20.4±1.5	292±3	6.66±0.20	6.3min
FS3	0.12±0.020	25.8±2.3	296±2	6.41±0.09	10.03min
FS4	0.10±0.012	33.6±3.64	258±3.51	6.73±0.05	19.16min
FP1	0.13±0.014	56.5±7.7	128±2.25	6.37±0.08	4.5min
FP2	0.12±0.020	54±7.8	132±3.05	6.83±0.19	3.03min
FP3	0.23±0.022	49±7.4	142±3.51	6.52±0.06	6.45min
FP4	0.19±0.016	43.5±8.2	121±2.29	6.49±0.05	11min
FV1	0.08±0.013	33±6.9	359±4.20	6.42±0.07	40sec
FV2	0.09±0.008	45.2±6.5	365±5.10	6.71±0.14	43sec
FV3	0.08±0.008	66.6±5.2	348±5.27	6.41±0.09	83sec
FV4	0.10±0.018	62.3±3.9	360±4.31	6.81±0.24	110sec
FC1	0.15±0.037	53±2.8	367±4.19	6.53±0.17	118sec
FC2	0.11±0.011	46±3.2	371±4.56	6.39±0.08	109sec

Table 3: Evaluation parameters of all Formulations

Formulation Code	Moisture content ±SD (%)	Moisture uptake ±SD (%)	Drug content ±SD (%)	Tensile Strength ±SD (%)	VTR ±SD ($mg/cm^2/hr$)
FS1	3.33±0.010	3.1±0.05	99±0.003	148.6±1.6	7.05±0.12
FS2	5.88±0.036	4.54±0.01	99.2.5±0.19	83.09±1.3	10.01±0.5
FS3	3.44±0.010	3.33±0.01	92.6±0.16	123.62±2.4	7.13±0.9
FS4	3.44±0.010	3.57±0.03	85.9±0.12	112.98±3.2	6.92±0.12

FP1	1.81±0.009	1.61±0.20	97±0.04	132.26±2.8	8.05±0.45
FP2	5.55±0.020	2.04±0.08	95.3±0.19	98.01±2.4	9.09±0.68
FP3	2.5±0.015	2.43±0.09	83.6±0.006	88.35±2.6	5.98±0.19
FP4	1.69±0.013	2.85±0.01	90.7±0.31	141.78±1.7	8.19±0.23
FV1	3.03±0.024	3.03±0.12	97.5±0.25	102.12±1.2	8.68±0.27
FV2	2.85±0.019	2±0.02	90.6±0.21	145.88±0.92	6.53±0.34
FV3	2.12±0.012	1.42±0.17	94±0.20	119.64±1.7	5.82±0.67
FV4	2±0.010	4.5±0.03	97.2±0.007	129.06±2.3	7.89±0.98
FC1	3.22±0.028	1.48±0.09	96.9±0.01	86.78±2.1	8.89±0.63
FC2	1.96±0.008	1.96±0.14	98±0.02	95.21±3.4	8.54±0.51

Table 4: Cumulative % Drug Release of Formulation FS1-FS4 & FP1-FP4

TIME (MIN)	CUMULATIVE % DRUG RELEASE							
	FS1	FS2	FS3	FS4	FP1	FP2	FP3	FP4
1	16.2	7.2	23.4	39.6	23.4	48.6	55.8	7.2
2	32.4	23.4	48.6	55.8	39.6	64.8	72	32.4
4	64.8	81	81	72	72	81	81	72
5	90	97.2	97.2	90	97.2	97.2	90	97.2

Table 5: Cumulative % Drug Release of Formulation FV1-FV4 & FC1-FC2

TIME (SEC)	CUMULATIVE % DRUG RELEASE					
	FV1	FV2	FV3	FV4	FC1	FC2
0	0	0	0	0	0	0
20	23.4	7.2	16.2	7.2	32.4	23.4
40	39.6	16.2	32.4	32.4	64.8	48.6
60	64.8	32.4	48.6	64.8	81	55.8
90	81	64.8	55.8	81	90	72
120	97.2	97.2	90	97.2	97.2	97.2

Table 6: Release kinetic analysis dynamic method of all formulations

FORMULATION CODE	ZERO ORDER (R^2)	FIRST ORDER (R^2)	H. MATRIX (R^2)	HIX. CROW. (R^2)	BEST FIT MODEL	MECH. OF RELEASE
FS1	0.9938	0.8711	0.9110	0.9303	Peppas korsmeyer	Super case II transport
FS2	0.9705	0.8531	0.9391	0.9211	Peppas korsmeyer	Super case II transport
FS3	0.9903	0.8811	0.9203	0.9624	Peppas korsmeyer	Anomalous transport
FS4	0.9086	0.9321	0.9361	0.9560	Peppas korsmeyer	Fickian diffusion (H. matrix)
FP1	0.9940	0.7997	0.9087	0.9024	Zero order	Anomalous transport
FP2	0.8689	0.8803	0.9476	0.9434	Peppas korsmeyer	Fickian diffusion (H. matrix)
FP3	0.7507	0.9411	0.9714	0.8941	Peppas korsmeyer	Fickian diffusion (H. matrix)
FP4	0.9859	0.7995	0.9328	0.8964	Zero order	Super case II transport
FV1	0.9729	0.9013	0.9151	0.9759	Peppas korsmeyer	Anomalous transport
FV2	0.9635	0.7506	0.9154	0.8454	Peppas korsmeyer	Super case II transport
FV3	0.9739	0.8400	0.8989	0.9065	Peppas korsmeyer	Anomalous transport
FV4	0.9595	0.9010	0.9383	0.9669	Hixon-crowell	Super case II transport
FC1	0.8534	0.9886	0.9385	0.9829	First Order	Anomalous transport

FC2	0.9671	0.8263	0.9114	0.9262	Peppas korsmeyer	Anomalous transport

Table 7: Stability study of optimized formulations

DAYS	% DRUG CONTENT				
	FS2	FP2	FV1	FC1	FC2
0	99.2.5±0.19	95.3±0.19	97.5±0.25	96.9±0.01	98±0.02
7	98.9±0.18	94.8±0.09	97±0.19	96.1±0.05	97.3±0.01
15	98±0.11	93.2±0.12	96.5±0.20	95.8±0.10	97.7±0.08
21	97.7±0.14	92.8±0.17	95.6±0.18	94.5±0.01	96.8±0.11
30	97.8±0.12	92.9±0.10	95.8±0.23	94.7±0.09	96.9±0.03

Fig.2: Thickness of all formulations

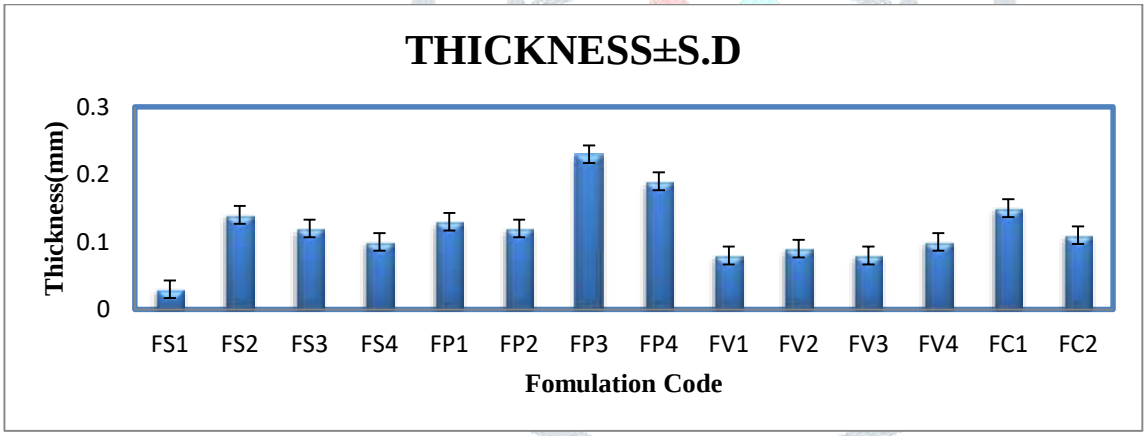


Fig.3: Folding endurance of all formulations

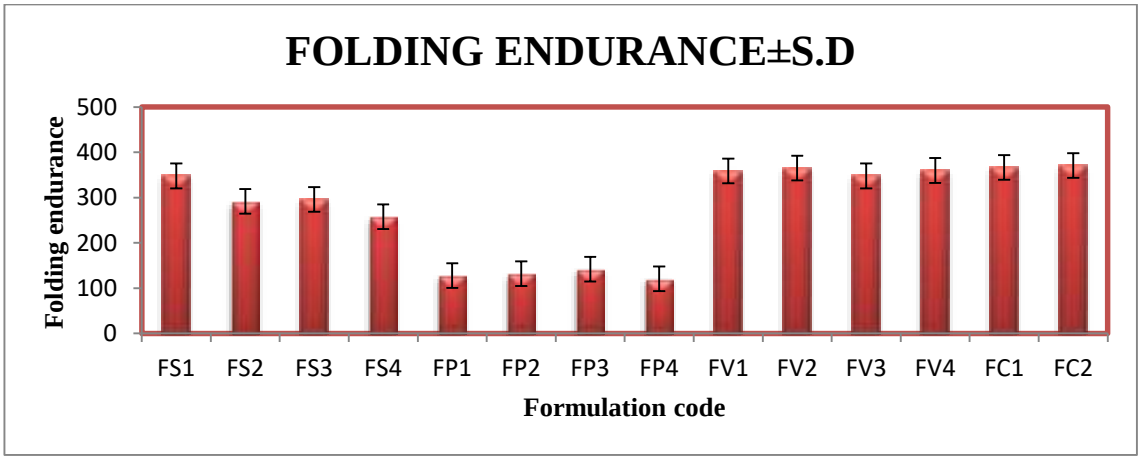


Fig.4: % Drug content of all formulations

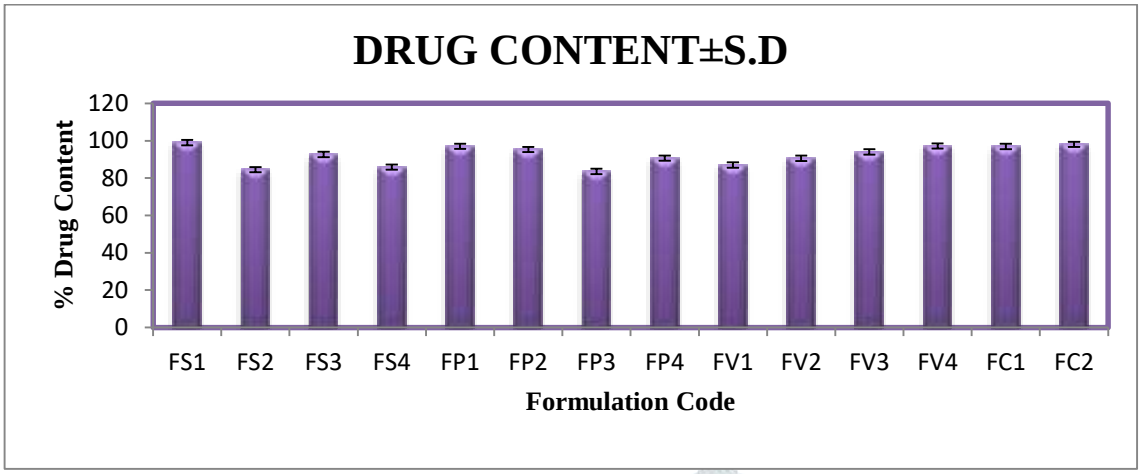


Fig.5: Zero order release profile of formulation FS2

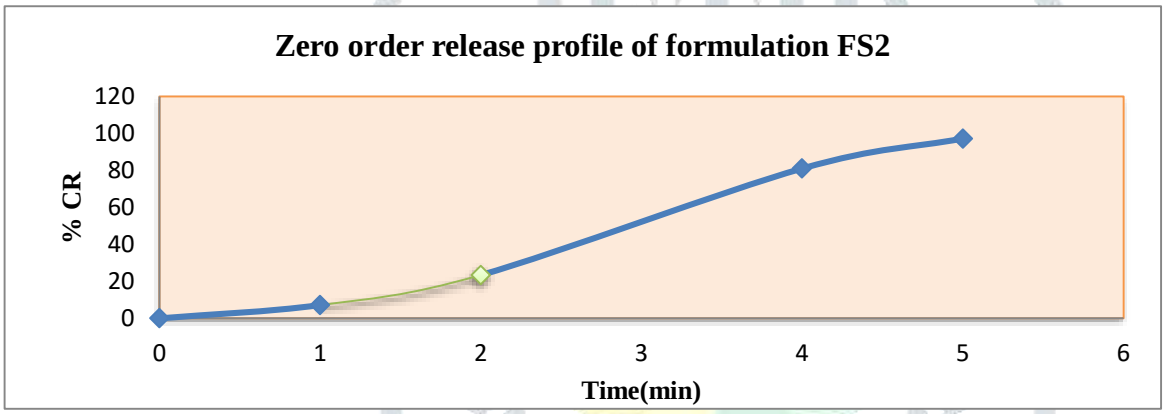


Fig.6: Zero order release profile of formulation FP2

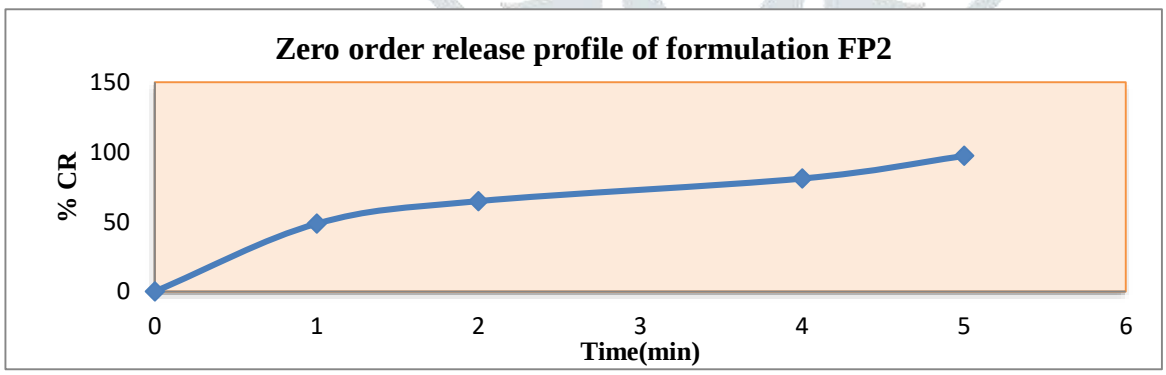


Fig.7: Zero order release profile of formulation FV1

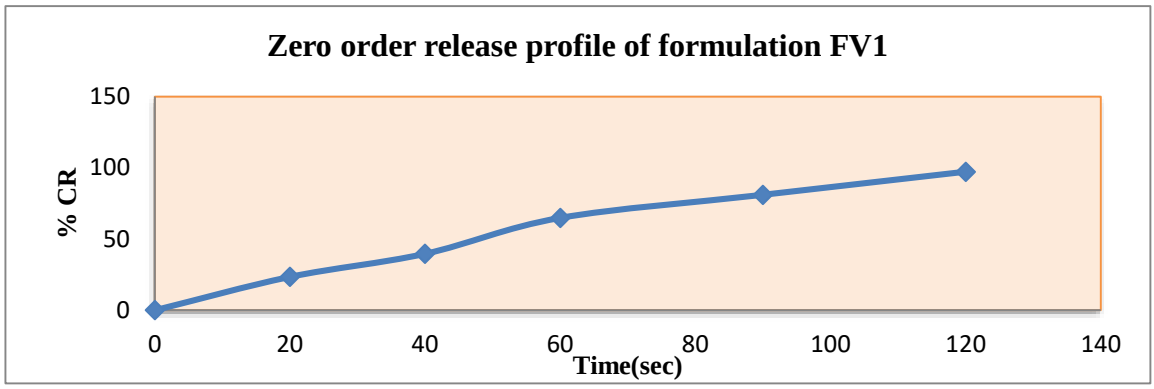


Fig.8: Zero order release profile of formulation FC1

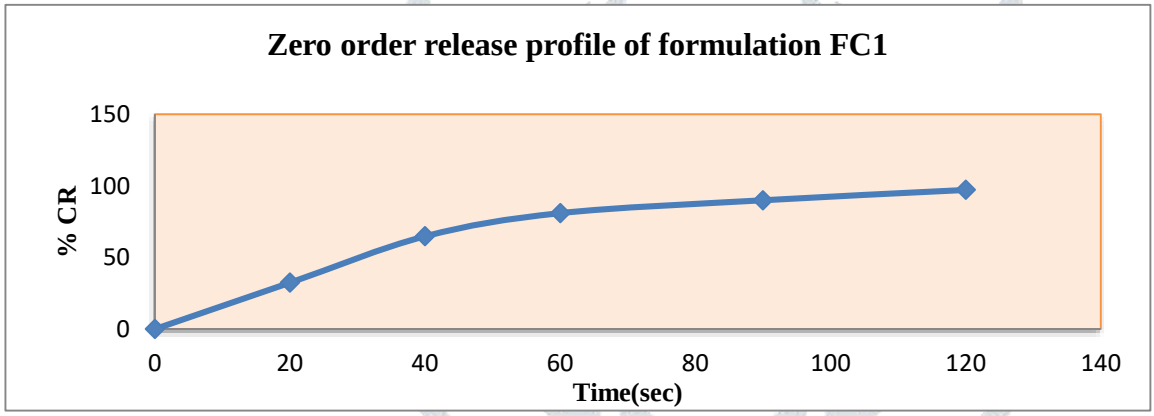
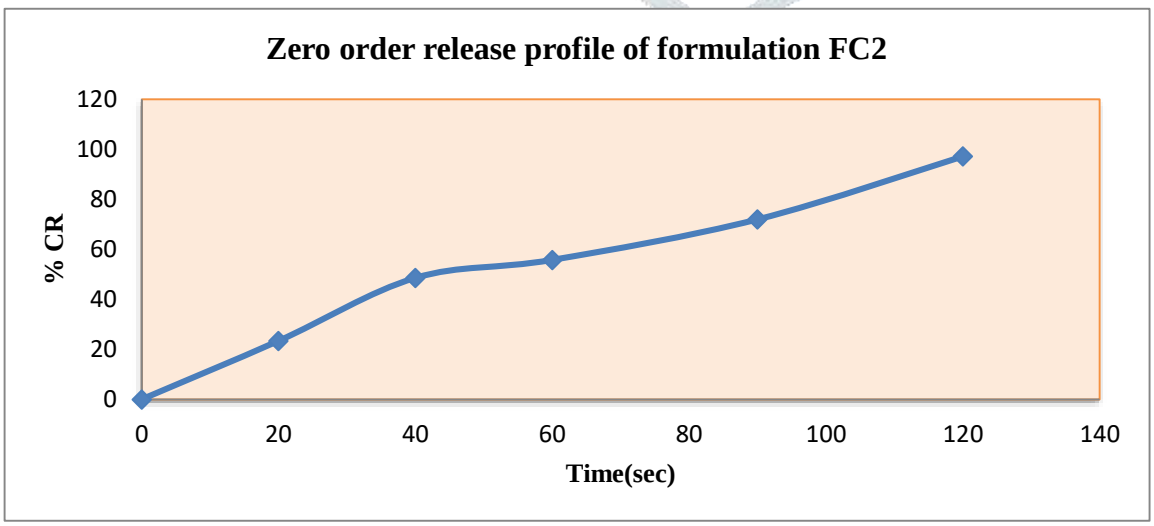


Fig.9: Zero order release profile of formulation FC2



4. Conclusion

Buccal delivery is a growing technology and recent advances in buccal dosage forms have been the advancement of adhesive tablets, gels, ointments, patches and more recently fast mouth dissolving polymeric films. The main purpose of research work was to design and evaluate oral fast dissolving thin strips loaded with Donepezil HCl.On the basis of current research work it had been concluded that formulated Oral fast dissolving thin strips may be used as an effective tool for buccal drug delivery of Donepezil Hydrochloride.

The prepared oral fast dissolving strips were effectively useful for the treatment of Alzheimer disease. As a fast dissolving formulation it can be easily administer and it dissolved in buccal cavity. It is an effective dosage form for geriatric patients because they have swallowing problem. Donepezil HCl is used as a pure drug in the formulations it has long half-life i.e. ~72 hours. So it remains in the body for long duration and shows an effective result in Alzheimer patients.

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