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FORMULATION AND EVALUATION OF ORAL FAST DISSOLVING FILM OF CINNARIZINE

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Abstract:
Cinnarizine is a H_1 anti-histaminic drug and it can be used in the treatment of nausea, vomiting, motion sickness, vertigo and in menier's disease. The purpose of present work was a development of fast dissolving oral film of cinnarizine, to overcome the limitation of current routes of administration to provide faster dissolution rate and increase the patient compliance. The amount of dose of drug calculate according to the area covered by the 15ml formulation without drug. The amount of drug was then used for the preparation of film by using solvent casting method utilizing HPMC E5 as a film forming polymer and PEG 400 as a plasticizer. The 3^2 factorial design was applied for optimization of concentration of polymer HPMC E5 and plasticizer PEG 400. The prepared film were evaluated for various parameters like film thickness, folding endurance, drug content, dispersion test, uniformity of weight, surface pH measurement, moisture loss study, in vitro drug dissolution study, disintegration time and stability study.in vitro drug dissolution studies were carried out using simulated salivary fluid (pH 6.8 phosphate buffer).among all the formulation, formulation (F5) which contain HPMC E5 (15%)and PEG400(6%) were released upto 98.17% of the drug from the film within 25 sec. which exhibit faster absorption and also shows desirable characteristics of film than other formulation.

Keywords: *Oral fast dissolving film, cinnarizine, motion sickness, menier's disease, HPMC E5, PEG 400, solvent casting method.*

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INTRODUCTION:

Cinnarizine is chemically 1-benzhydryl 1-4-cinnamyl piperazine. It acts as histamine H1 antagonist and calcium channel blocker. It bind to histamine H1 receptor and to muscarinic acetylcholine receptor. Cinnarizine also inhibit contraction of vascular smooth muscle cells by blocking calcium channels. It is used for the treatment of nausea, vomiting, vertigo, motion sickness, menier's disease. Among all the routes of drug administration the oral route is most advisable route in the designing the formulation of dosage form than drug delivery design by other routes of administration. The oral mucosa is conveniently and easily accessible and therefore allows uncomplicated application of various dosage form. Furthermore, the oral mucosa is robust against local stress or damage and shows fast cellular recovery. Active substances can be administered locally to treat oral diseases such as periodontal disease, fungal, bacterial infection.

A systemic action can be achieved via drug permeation through the mucosal epithelium. The concept of fast dissolving drug delivery emerged from the desired to provide patient with more conventional means of taking that medication. Fast dissolving films recently have acquired great importance in the pharmaceutical industry due to their unique property and specific advantages like no need of water for disintegration, accurate dosing, rapid onset of action, easy of transportability, easy of handling, pleasant taste and improve the patient compliance. Fast dissolving oral film are useful in the patient such as pediatric, geriatric, bedridden, emetic patient, diarrhea, sudden episode of allergic attack or coughing for those who have an active life style. It is also useful whether local action desired such as local anaesthetic for toothache, oral ulcer, cold sore or teething.

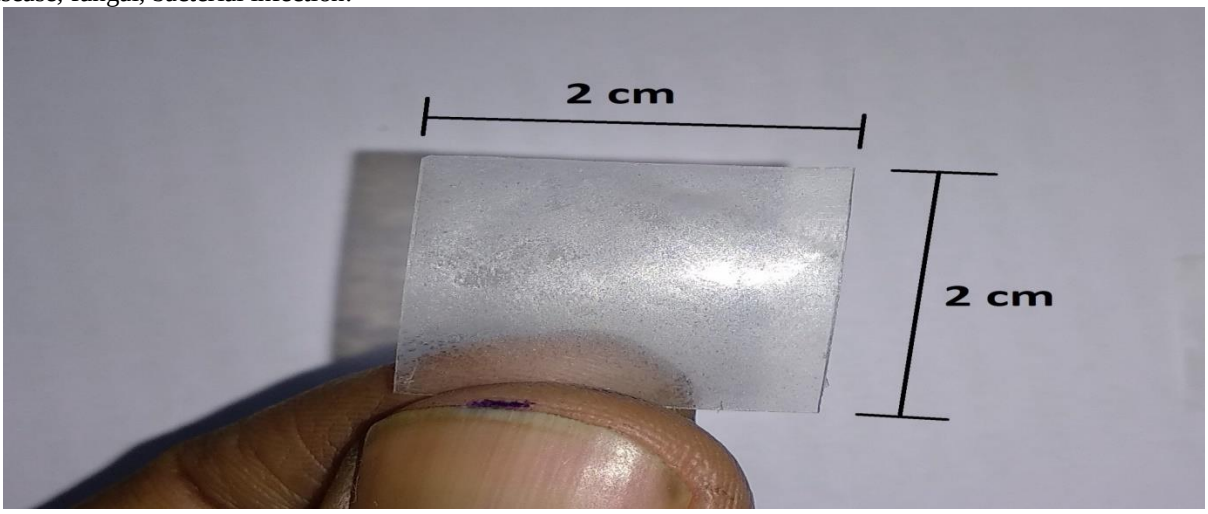

Fig 1: cinnarizine loaded oral fast dissolving film.

MATERIAL AND METHODS:

Table 1: List of chemicals

Sr.no.	Name of chemicals	use
1	Cinnarizine	In the treatment of Motion sickness, menier's disease, nausea, vomiting.
2	HPMC E5	polymer
3	PEG 400	plasticizer
4	Citric acid	Buffering agent
5	Mannitol	Sweetning agent
6	Pipermint oil	Flavouring agent
7	Water	Solvent

Table 2: List of instruments

Sr.no.	Name of instrument	Model/Manufacturer
1	Analytical weighing balance	Labine analytical balance,Mumbai
2	Magnetic stirrer	Remi equipment, Mumbai
3	Sonicator	Bio-techniques,Mumbai
4	Film former	V.J.instrument,Mumbai
5	Franz diffusion cell	Orchid
6	Digital pH meter	Hanna instrument
7	UV spectrophotometer	Jasco

Preparation of fast dissolving oral films

1)Calculation of drug loaded in film

15 ml of placebo formulation (without drug) which can be covered the 10×30cm=300 cm^2 area. i.e.10cm-width of film and 30cm-length of the film.

Now dose of cinnarizine is 25mg in 2×2cm film i.e.4cm^2 area.

Then the 4cm^2→25mg drug

300cm^2→ 'x' mg of drug

X=300×25/4

X=1875 mg of drug

Hence the 1875 mg of drug required in 15ml formulation.

2)Procedure

Solvent casting method

Polymer HPMC E5 (1400mg, 1500mg, 1600mg) were weight accurately and dispersed in water according to different formulation as shown in table 3. Then add plasticiser (0.4ml, 0.5ml, 0.6ml) for different formulation (f1 to f9) which shown in table 3 and mixed well till clear solution was obtained. Then the drug was added to the polymeric solution. Remaining ingredient citric acid, mannitol, pipermint oil are add and then continuously stirring for 15 minute in the magnetic stirrer. After that the solution is placed on the ultrasonicator for 30 minute, to remove the air bubble from the formulation. After that clear solution can be pour on the film former with the help of dragger with the maintaining specific thickness 0.4mm. film former temperature maintained at 40ºc. after that film allow to dry, then the dried film were carefully removed from the film former, checked in any imperfection or air bubbles and cut to pieces of 2×2cm i.e. 4cm^2.

Table 3: Composition of factorial design formulations of cinnarizine of different batches

Batch	Drug (mg)	HPMC E5 (mg)	PEG 400 (ml)	Citric acid (mg)	Mannitol (mg)	Pipermint oil (ml)	Water (ml)
F1	1875	1400 (14%)*	0.5ml (5%)*	200	200	0.5	10
F2	1875	1500 (15%)*	0.5ml (5%)*	200	200	0.5	10
F3	1875	1600 (16%)*	0.5ml (5%)*	200	200	0.5	10
F4	1875	1400 (14%)*	0.6ml (6%)*	200	200	0.5	10
F5	1875	1500 (15%)*	0.6ml (6%)*	200	200	0.5	10
F6	1875	1600 (16%)*	0.6ml (6%)*	200	200	0.5	10
F7	1875	1400 (14%)*	0.7ml (7%)*	200	200	0.5	10
F8	1875	1500 (15%)*	0.7ml (7%)*	200	200	0.5	10
F9	1875	1600 (16%)*	0.7ml (7%)*	200	200	0.5	10

*Polymer and plasticiser concentration in percentage

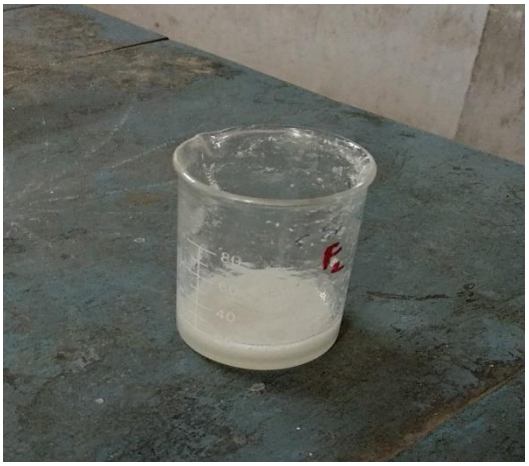

Fig.2: Initial mixture of all ingredient

Fig. 3: Formulation place in ultrasonicator to remove air bubble

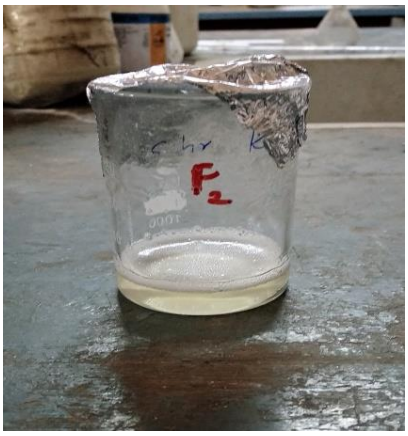

Fig. 4: Formulation after the ultrasonicator clear solution form

Fig. 5: Film former

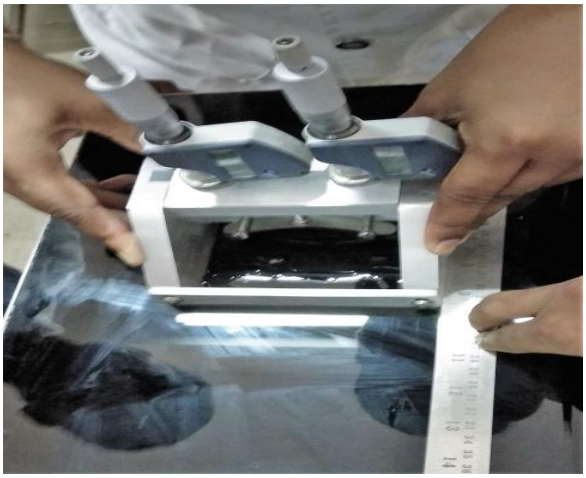

Fig. 6: Formulation pour on the film former

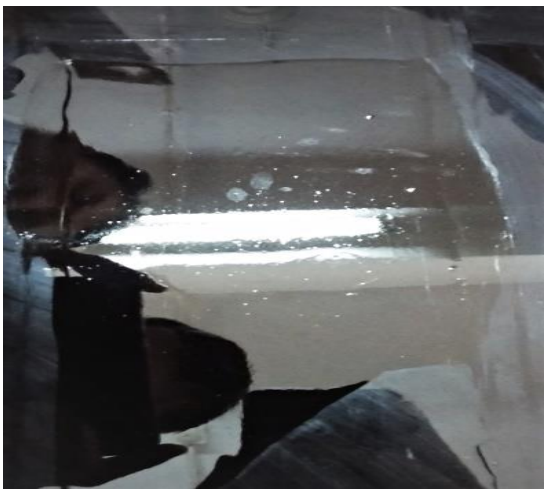

Fig. 7: Formulation spread on the film former

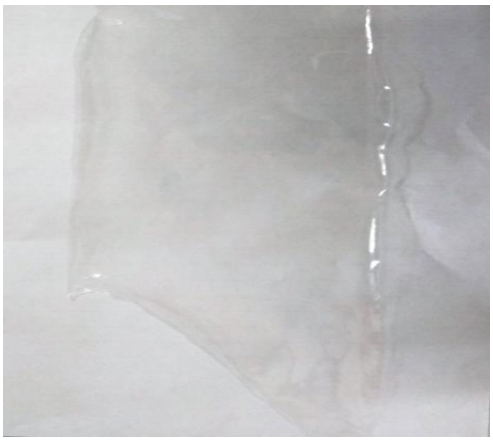

Fig. 8: After the drying film removed from the film former

Fig. 9: Film cut into 2×2cm

Evaluation of oral fast dissolving film of cinnarizine

Film thickness

A thickness of the film was calculated by using digital vernier caliper. Film was measured at five position i.e. central and four corners and the mean thickness was calculated.

Folding endurance

Folding endurance was determined repeatedly by folding a small strip of the film at the same place till number of times the film could be folded at the same place without cracking was noted as folding endurance. The film was folded at an angle of 180º at the same place till it broke or folded up to 100 times without breaking. The studies were performed in trice and the average mean was calculated.

Drug content

Drug content of all the batches was determined by UV spectrophotometric method. For this 2×2cm strip from each batch was cut and dissolve in 50ml of phosphate buffer pH 6.8. then the solution was filtered through whatman filter paper and diluted if necessary. The resulting solution was measured spectrophotometrically at 253nm.

Uniformity of drug content

For determining the uniformity of drug content in the film 10 films were taken and assayed same procedure was repeated for the batches as above.

Dispersion test

A film equivalent to 25mg of cinnarizine was placed in 200ml of 6.8 pH phosphate buffer and was stirred for 3 minutes. Then the resulting solution was passed through sieve number 22. The film passed the dispersion test only when no residue is left on the screen.

Uniformity weight

Three films were randomly selected and weight individually, then the mean weight and standard deviation of films was calculated. It is desired that films should have nearly constant weight. It is useful to ensure that a film contains the proper amount of excipient and API.

Surface pH measurement

The surface pH of film was determined in order to investigate the possibility of any side effects in vivo. As an acidic an alkaline pH may cause irritation to the oral mucosa. It is determined to keep the surface pH as close to neutral as possible. Film is slightly wet with the help of water. The pH is measured by using digital pH meter to determined the surface pH. The procedure was performed in triplicate and average with standard deviation was calculated.

Moisture loss studies

The percent moisture loss study was carried out to check the physical stability and integrity of the films. In the present study the moisture loss capacity of the film was determined by placing the known weight and predetermined size of the film in desiccator containing anhydrous calcium chloride for three days. The film were removed and reweight and the percent moisture loss of the films was measured by using following formula.

Percent moisture loss = initial weight – final weight /final weight ×100

***In vitro* drug dissolution study**

In vitro drug dissolution studies were performed on all the film formulation by using an apparatus called franz diffusion cell apparatus maintained a volume capacity of 15ml was used for dissolution study. The film equivalent to 25mg of cinnarizine was placed in between the two compartment of an apparatus and pipette 15ml of 6.8 pH buffer (pH of saliva) was added to receptor compartment. Cell is kept on magnetic stirrer and bead in the cell is maintained at a speed of 50 revolution per minute and medium maintained at a temperature of nearly 32ºc ±0.5ºc and withdraw 1ml of sample at various time intervals and the sample were diluted with 6.8 pH phosphate buffer and measured absorbance at 253nm against 6.8 pH

buffer as blank. The various dissolution profiles for films were given in shown in figure 10 and the in vitro dissolution parameter were given in table number 6.

***In vitro* disintegration time**

The disintegration time reported was the time when the film starts to break. In vitro disintegration time was determined visually in a petri-dish containing 20ml of pH 6.8 phosphate buffer with swirling every 10 seconds.

Stability study

Accelerated (40ºc / 75% RH) and real time (30ºc / 65% RH) stability study was carried out as per ICH guidelines at time intervals 0,7,14,28,42,60 days. Film were evaluated for change in physical parameter, drug release and drug content. From the two months stability data it can be concluded that in F5 formulation there is no any significant change in the physical appearance, disintegration time, drug release, drug content compared with the initial data for 25mg strength. Stability profiles of formulation at different temperature are shown in table number 7.

RESULT AND DISCUSSION:

The prepared films of all formulation were evaluated and results shown in table number 4,5,6. weight of three films from all the formulation were determined individually. As the concentration of polymer increases, the weight of film also increases. All the batches were evaluated for thickness using digital vernier caliper. As the formulations contain different concentration of polymer, hence the thickness of the films was found in the range of 0.40 to 0.56 mm. the thickness increases with the increase in the concentration of polymer. The folding endurance was found to vary between 93 ±5 to 105 ±5 fold indicate that the films have good flexibility. The formulation with high concentration of polymer have low value of folding endurance because after specific increase in concentration of polymer decrease in folding endurance is observed due to film thickness. More thickness lower will be folding endurance

Disintegration time was found to vary between 25 to 35 second film prepared with the HPMC E5 (15% concentration) had shown fast disintegration as compared to other concentration. Drug content was evaluated and it varied in the range of 95.04±1.96 to 99.01±1.15. drug content was found to be low for F1 formulation i.e.93.15±1.05 and more for F5 formulation i.e. 99.01±1.15. as per the USP the drug content was found to be in the range of 85-115%.

Three film strips of 4cm^2 was cut from each film and estimated for uniformity of drug content using UV spectrophotometric method. It is observed that all the selected formulation was found to be content almost uniform quantity of drug as per content uniformity studies. The surface pH of all the selected formulation was ranging between 6.7 to 6.9, since surface pH of the film was found to be around neutral pH, there will not be any kind of irritation to the mucosal oral cavity. The moisture loss of all the selected formulation was measured. Out of all the selected formulation the film with HPMC E5 (15% concentration) polymer showed the lowest % moisture loss than other formulation and hence it is more stable than other. Accelerated stability also shows that F5 formulation there is no any significant change in the physical appearance, disintegration time, drug release, drug content compared with the initial data from the two month stability data.

Table 4: Evaluation of oral fast dissolving film of cinnarizine of all batches

Formulation code	Film thickness (mm)*	Folding endurance	Drug content (%)*	Dispersion test
F1	0.45 ± 0.004	105 ± 5	95.04 ± 1.96	Passed
F2	0.52 ± 0.006	102 ± 5	96.12 ± 1.12	Passed
F3	0.55 ± 0.008	99 ± 5	96.20 ± 0.94	Passed
F4	0.51 ± 0.004	104 ± 5	95.15 ± 1.05	Passed
F5	0.40 ± 0.004	100 ± 5	99.01 ± 1.15	Passed
F6	0.56 ± 0.008	96 ± 5	97.05 ± 0.60	Passed
F7	0.52 ± 0.014	103 ± 5	96.25 ± 0.85	Passed
F8	0.55 ± 0.006	99 ± 5	97.10 ± 0.91	Passed
F9	0.56 ± 0.004	93 ± 5	96.23 ± 1.01	Passed

*All value are mean of three reading ± standard deviation

Table 5: Evaluation of oral fast dissolving film of cinnarizine of all batches

Formulation code	Uniformity weight (mg)*	Surface pH measurement*	% moisture loss*	Disintegration time (sec.)*
F1	61.11 ± 0.05	6.72 ± 0.050	2.18 ± 0.071	35 ±2.08
F2	60.31 ± 0.09	6.70 ± 0.045	2.63 ± 0.022	32 ±2.51
F3	63.33 ± 0.12	6.85 ± 0.078	3.01 ± 0.032	30 ±2.66
F4	62.26 ± 0.09	6.72 ± 0.035	2.75 ± 0.041	31 ±1.55
F5	65.30 ± 0.15	6.80 ± 0.024	1.15 ± 0.012	25 ±1.21
F6	64.41 ± 0.16	6.85 ± 0.030	1.90 ± 0.032	28 ±1.91
F7	61.10 ± 0.11	6.90 ± 0.027	2.01 ± 0.015	33 ±1.88
F8	60.20 ± 0.10	6.79 ± 0.045	2.25 ± 0.019	29 ±2.21
F9	63.31 ± 0.13	6.75 ± 0.041	3.12 ± 0.042	27 ±2.11

*All value are mean of three reading ± standard deviation

In vitro drug release data

The result indicate that the best release among formulations containing HPMC E5 (15%) i.e. 98.17%. formulation F5 showed better release. The result are shown in table number 6.

Table 6: In vitro cumulative % drug release in phosphate buffer pH 6.8

Time (sec.)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
10	18.862	19.391	21.086	19.608	22.203	21.869	18.055	20.121	21.250
20	24.869	23.230	24.631	22.560	30.320	28.450	25.050	24.051	26.203
30	30.251	29.300	31.720	29.161	35.710	31.660	32.460	31.424	30.121
40	35.151	36.210	36.271	34.330	40.631	37.721	36.505	38.545	37.567
50	41.576	42.710	43.121	42.203	50.302	43.032	45.157	46.931	46.802
60	48.731	49.216	49.410	48.321	58.424	52.450	51.610	53.710	52.210
70	56.203	57.215	56.299	55.801	68.310	61.211	60.450	62.171	60.236
80	65.161	67.312	68.140	65.199	79.315	71.161	61.500	69.642	70.750
90	72.330	74.411	76.512	73.213	86.110	80.550	78.620	79.893	80.564
100	80.141	81.412	83.130	82.031	92.130	88.230	85.660	86.792	87.632
110	86.310	88.130	90.213	85.413	98.171	94.840	93.105	95.801	96.123

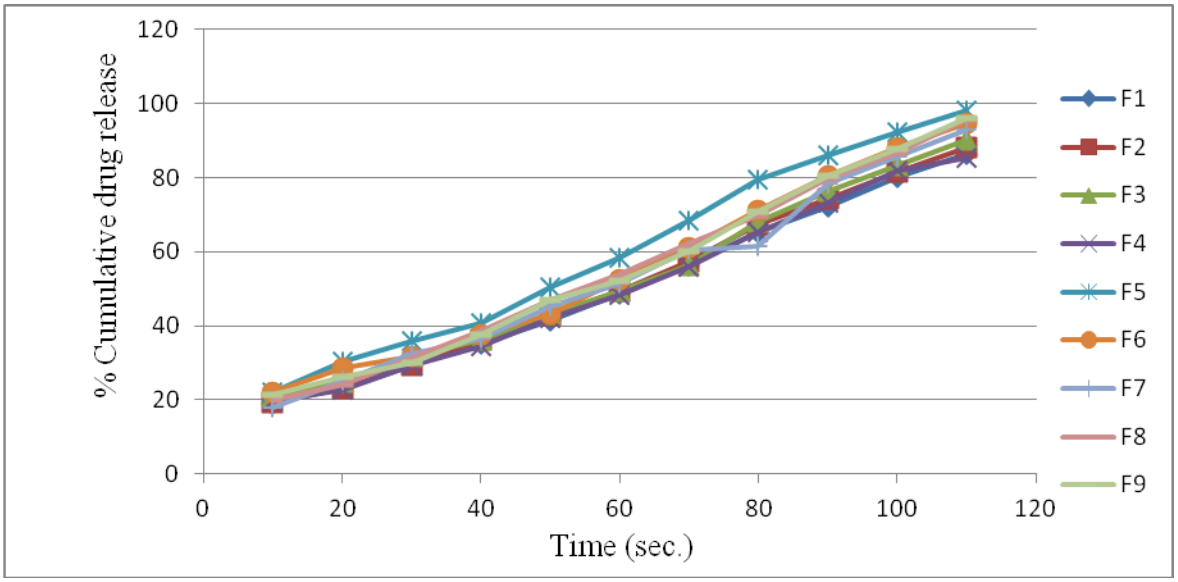

Fig. 10: % cumulative drug release from formulation F1 to F9

Stability profile of formulation F5 at different temperature

Table 7: Stability profile of formulation F5 at different temprature

Time in days	Real time (30ºc / 65% RH)		Accelerated (40ºc / 75% RH)	
	% drug release	Drug content (mg)	% drug release	Drug content (mg)
0	96.13	25	96.13	25
7	96.06	24.95	96.04	24.94
14	95.97	24.87	95.96	24.84
28	95.89	24.80	95.85	24.72
42	95.73	24.72	95.74	24.48
60	95.66	24.63	95.62	24.25

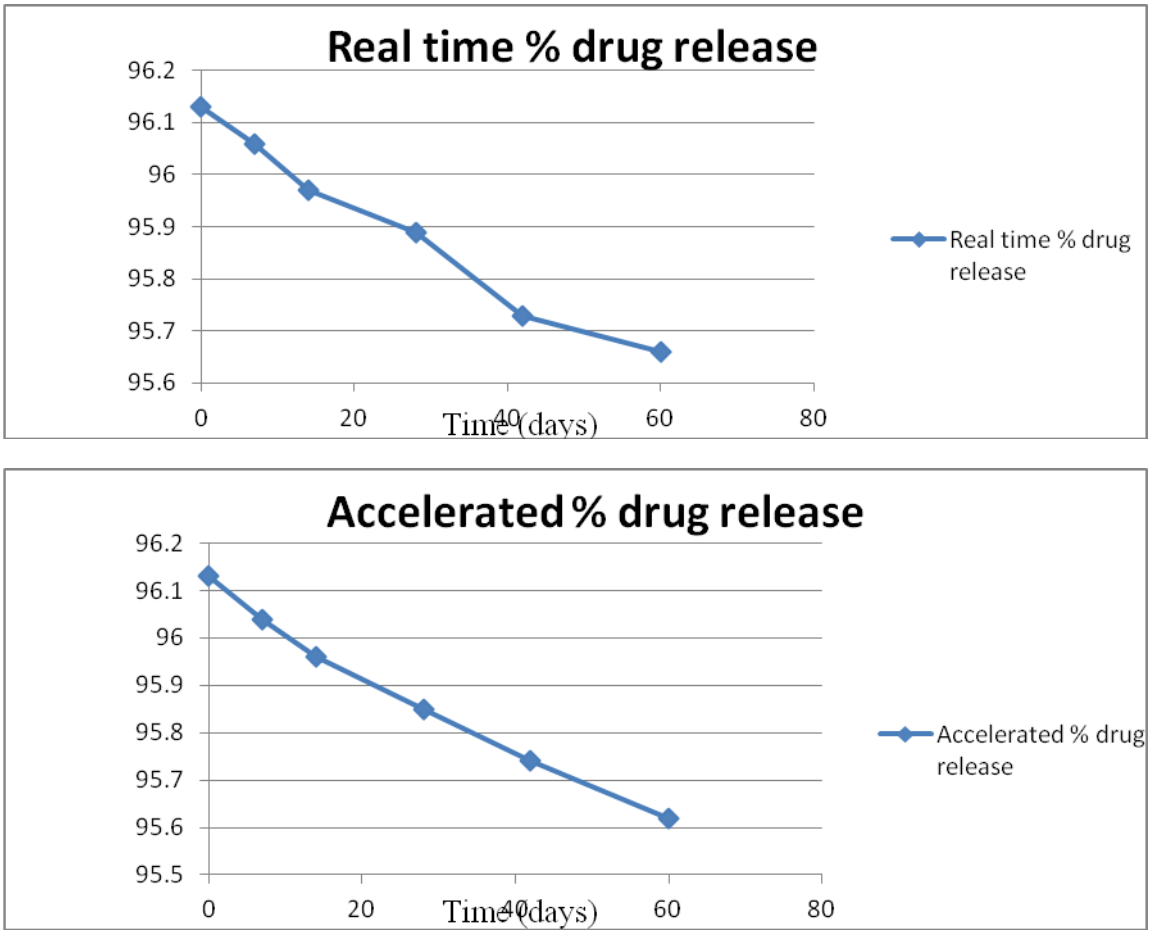

Fig. 11: Showing % drug release at Real and Accelerated time.

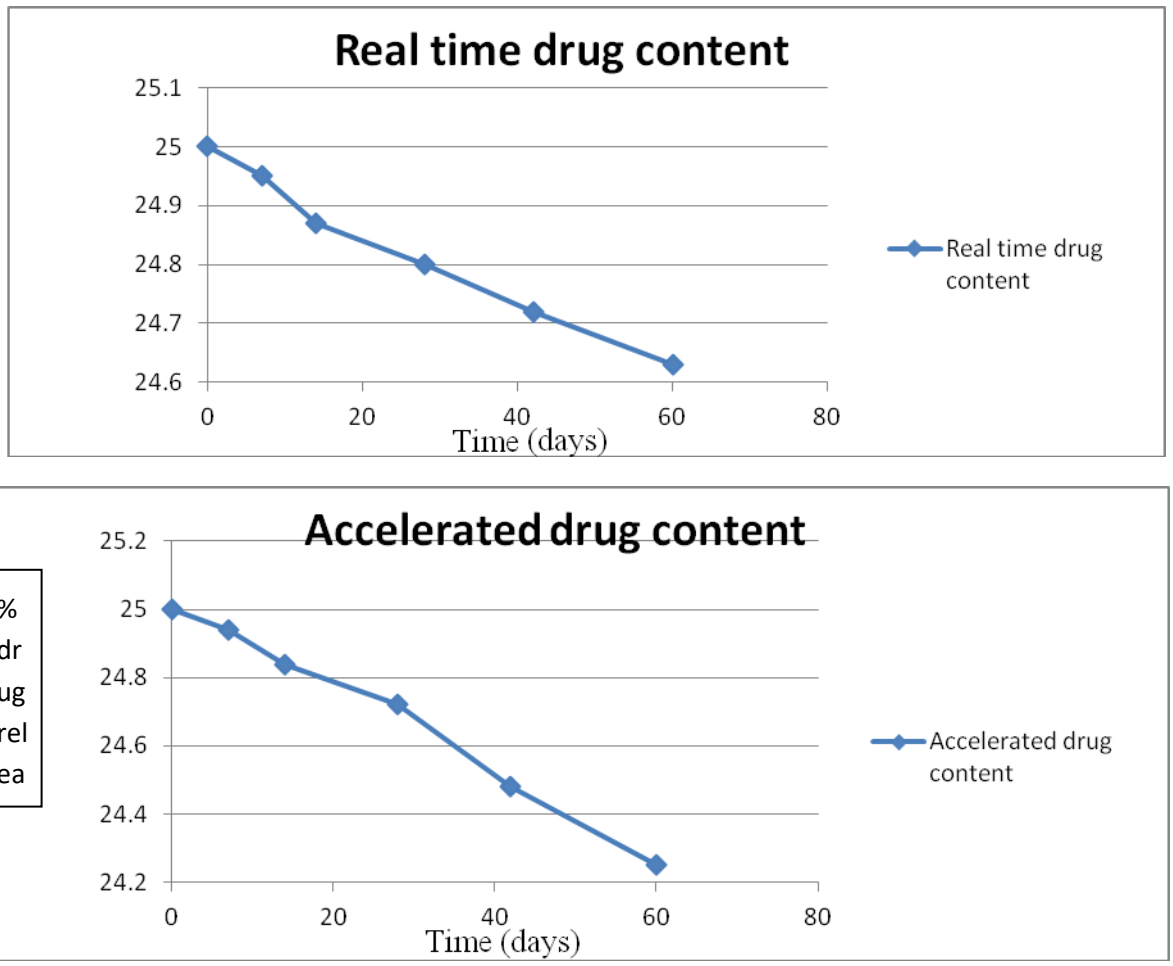

Fig. 12: Showing drug content in Real and Accelerated condition.

CONCLUSION:

Oral fast dissolving film of cinnarizine were prepared by solvent casting method using HPMC E5 as polymer that rapidly dissolves film in the oral cavity and delivering the drug to the systemic circulation. Plasticiser PEG 400 used to enhance the flexibility of the strip and reduces the brittleness of the strip. The formulation F5 which contain HPMC E5 (15%) and plasticiser PEG 400 (6%) which satisfied all parameters of fast dissolving films as compare to other films and appears to be promising would be able to offer benefits such as rapid drug release, good disintegration time and acceptable physicochemical characters and thereby may help to improve bioavailability of the drug.

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