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Design and Characterization of Fast Dissolving Buccal Films of Paroxetin

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ABSTRACT

Depressive Disorder medications are pharmacological agents that are used to treat Major Depressive Disorder disease. The intention of the present study is to design and characterization of fast dissolving buccal films of Paroxetin. Films were prepared by using different polymers like HPMC E15, PVA, PVP and Glycerol as plasticizer and saccharin as a sweetening agent and vanillin as a flavoring agent. Buccal films were prepared using solvent casting technique. The major problem with Paroxetine was it belongs to class Ⅱ in BCS classification and have low solubility in biological fluids. In order to enhance the solubility of Paroxetine solid dispersion of Paroxetine were prepared by melting technique at different drug carrier (PEG 4000) weight ratios and evaluated. No interaction was found between the drug and the polymers which was obtained by FTIR studies. The buccal films were evaluated for Folding endurance, weight variation, Drug content, Thickness, permeation study and *in-vitro* drug release study. Dissolution profile were studied by using USP dissolution apparatus type I, pH 6.8 simulated saliva were used as dissolution media. The influence of variable like polymer type, and their concentration, on Paroxetine release profile was studied. The formulation was optimized on the basis of various evaluation parameters like drug content and *In-vitro* drug release. Formulation F3 successfully gave the fast release of drug within 12 minutes. Stability studies were as per ICH guide lines and result indicated that the selected formulation was stable.

Keywords: Paroxetine, HPMC E15, PVA, PVP, PEG 4000, Solvent casting method.

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INTRODUCTION

According to WHO, Depression is a common mental disorder that presents with depressed mood, loss of interest or pleasure, decreased energy, feelings of guilt or low self-worth, disturbed sleep or appetite, and poor concentration. Moreover, depression often comes with symptoms of anxiety. These problems can become chronic or recurrent and lead to substantial impairments in an individual's ability to take care of his or her everyday responsibilities. At its worst, depression can lead to suicide. Almost 1 million lives are lost yearly due to suicide, which translates to 3000 suicide deaths every day. For every person who completes a suicide, 20 or more may attempt to end his or her life.

However, the fear of taking solid tablets and the risk of choking for certain patient population still exist despite their short dissolution/disintegration time. Recent development in novel drug delivery system aims to enhance safety and efficacy of drug molecules by formulating a convenient dosage form for administration. One such approach is rapidly dissolving film. It consists of a very thin Buccal strip, which releases the active ingredient immediately after uptake into the Buccal cavity. Rapid film combines all the advantages of tablets (precise dosage, easy application).

Advantages of buccal films:

- No fear of obstruction or chocking.
- No need of water during film administration.
- Reduction in dose of the drug.
- Taste masking
- Improved patient compliance.
- Enhanced stability

MATERIALS AND METHOD

Paroxetine purchased from Balaj drugs, Hydroxypropyl methyl cellulose (HPMC E15), polyvinyl alcohol (PVP), and Polyvinyl pyrrolidone (PVP), were procured from Yarrow chemicals. All other chemicals used were of analytical grade.

Standard Curve of Paroxetine:

Paroxetine is a white fine powder which was soluble in simulated saliva pH 6.8. Though several methods are reported for its estimation, the UV spectrophotometric method was employed in the study. Paroxetine shows maximum absorbance at 293 nm in simulated saliva pH 6.8. Based on this information, a standard graph was constructed (Figure 1)

FTIR STUDIES:

FT-IR spectra of pure Paroxetine, and combination with HPMC E15, PVA, PVP, and PEG 4000

were showed in (Figure 2-6) Pure Paroxetine showed principle absorption peaks at 3500 cm^{-1} (N-H Stretch) and 1200-700 cm^{-1}(C-C Stretch), 1300-100 cm^{-1} (C-O Stretch), 2965-2850 cm^{-1}(C-H Stretch), Same peak of C-O Stretch, C-C Stretch, C-H Stretch, and N-H Stretch bonds were present as that of pure drug without much shifting in the spectra of Paroxetine along with the polymers. This recommended that there was no chemical interaction between the drug and polymers.

Preparation of Paroxetine solid dispersion:

Paroxetine and PEG 4000 are mixed using mortar and pestle. PEG 4000 as carrier in different proportions 1:2 (drug: carrier) as shown in (Table 2). To accomplish a homogenous dispersion the mixture is heated at or above the melting point of all the components with constant stirring. It is then cooled to acquire a congealed mass. It is crushed and sieved.

Characterization of Paroxetine solid dispersion:

1. Percentage Practical Yield:

Percentage practical yield is calculated to know about percent yield, thus its help in selection of appropriate method of production. Solid dispersions were collected and weighed to determine practical yield (PY) from the following equation (Figure 7)

Percentage of practical yield = Practical yield/ Theoretical yield x 100

2. Drug content:

10 mg of solid dispersions were weighed accurately and dissolved in 10 ml of methanol. The solution was filtered, diluted suitably and drug content was analyzed at 293 nm by UV spectrophotometer. Each sample analyzed in triplicate (Figure No.8). Actual drug content was calculated for all batches using the equation as follows

Percentage of drug content = Observed value/ Actual value x 100

Drug-polymer interaction study of films:

There is always a possibility of drug-excipients interaction in any formulation due to their intimate contact. The technique employed in this study to know drug- excipients interactions is IR spectroscopy. IR spectroscopy is one of the most powerful analytical techniques which offer the possibility of chemical identification. Infra-red spectra of pure drug Paroxetine and formulations were scanned by using FTIR, by a thin film method.

Evaluation of Paroxetine buccal films:

a) Physical appearance and surface texture of films:

This parameter was analyzed simply with visual inspection of films and evaluation of texture by feel or touch.

b) Weight uniformity of films:

Three films of the size 2×2 cm was weighed individually using digital balance and the average weights were calculated.

c) Thickness of films:

Thickness of the films was measured using screw gauge with a least count of 0.01mm at different spots of the films. The thickness was measured at three different spots of the films and average was taken.

d) Folding endurance of patches:

The flexibility of films can be measured quantitatively in terms of what is known as folding endurance. Folding endurance of the films was determined by repeatedly folding a small strip of the films (approximately 2x2 cm) at the same place till it broke. The number of times films could be folded at the same place, without breaking gives the value of folding endurance.

e) Drug content uniformity of films:

The films were tested for drug content uniformity by UV Spectrophotometric method. Films of 2×2 cm size were cut from three different places from the casted films. Each film was placed in 100 mL volumetric flask and dissolved in simulated saliva pH 6.8 and 5 mL is taken and diluted with water up to 10 ml. The absorbance of the solution was measured at λ max 293 nm using UV/ visible spectrophotometer (Shimadzu). The percentage drug content was determined.

f) *In-vitro* dissolution studies:

The release rate of Paroxetine Buccal films was determined by using USP dissolution testing apparatus I at 50 RPM. The film with 2×2 cm was placed in the 300 mL of 6.8 pH simulated saliva as dissolution medium, and temperature was maintained at 37°C. From this dissolution medium, 2 mL of the sample solution was withdrawn at different time intervals. The samples were filtered through Whitman filter paper and absorbance was determined 293nm using double beam UV-Visible spectrophotometer.

g) Permeation study:

The prepared Buccal films are placed in the diffusion cell on the upper membrane of the (donor compartment) and the receptor compartment contain a simulated saliva (20 ml) it can be contact with the dialysis membrane upper side of the donor compartment contain a film attach the film of length and width (2×2) cm it contain10 mg of drug. And the receptor compartment it contain a simulated saliva and magnetic bead and this diffusion compartment placed in the magnetic stirrer the drug permeation start through the dialysis membrane and enter in to the receptor compartment the drug to be enter in the receptor compartment and this solution taken 2 ml at regular time intervals and

maintain the sink condition by replace the 2ml of simulated saliva in to the receptor compartment and this every interval taken samples analyzed by (Shimadzu) UV-visible spectrophotometer.

h) Stability studies:

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors. To assess the drug and formulation stability, stability studies were done as per ICH guidelines. The formulated Buccal films were wrapped in aluminum foil and stored at 45 ± 0.5ºC for period of twelve weeks. After the period of three month, films were tested for appearance, drug content and *In-vitro* drug release.

RESULTS AND DISCUSSION:

Among the two formulations of solid dispersions i.e. A1 and A2, the formulation A2 was found to be better, which has shown maximum drug content and percentage drug release compared to A1 formulation. Based on the above study report solid dispersions of Paroxetine: Poly ethylene glycol 4000 solid dispersions (Paroxetine: PEG 4000) at ratio of 1:2 was selected for this study. It was proposed to formulate fast release buccal films and to evaluate the efficacy of PEG 4000 on solid dispersions. The formulated films were appeared to be clear, homogeneous; some are transparent and some are partially transparent. They were found be physically flexible and dry. The folding endurance was measured manually, by folding the films repeatedly at a point till it broke. The breaking time was considered as the end point. Folding endurance was found to be highest for F6 and lowest for F8. It was found that the folding endurance of the film was affected with increase of carrier concentration. The folding endurance values of the films were found to be optimum and therefore, the films exhibited the good physical and mechanical properties. The folding endurance of films was found to be in the range of 316 to 353(Table No.5).

As all the formulations contain different amount of polymers, the thickness was gradually increased with the amount of polymers. All the film formulations were found to have thickness in the range of 0.15 to 0.23 mm and were observed within the limits.

Weight variation:

The randomly selected film strips about 2 × 2 cm areas were cut at different places from the casted film and weight was measured. Weight of film strip units varies from 46.21 to 52.05 mg. The results indicated that selected carriers used in method of solid dispersion preparation, proportion of carrier used have reduced the variation and improved the uniformity of the distribution in casted films (Table No.5). It was observed that *in vitro* dissolving/disintegration time varies from 32.67 to 47.33 sec for all the formulations (Table 5). *In vitro* disintegration time of films was affected by polymers

viz. HPMC E 15, PVA and PVP. This is due to polymer's high-water absorption and retention capacities.

Drug content:

The prepared film formulations were studied for their drug content. The drug was dispersed in the range of 91.77 % to 97 .43 %. Suggesting that drug was uniformly dispersed in all films.

***In vitro* dissolution studies:**

The in-vitro drug release profiles of the formulations in simulated saliva pH 6.8 show differences depending on their composition. The rate of drug release from the HPMC E 15 films was significantly higher than the films containing PVP and PVA (Figure 8). The formulation F3 films containing a HPMC E 15 showing high percentage of drug release (97.41%) within 12 min compare to that of films containing PVP and PVA as a polymer.

Table 1: Calibration curve of Paroxetine

Sl. No	Concentration (µg/mL)	Absorbance at 293 nm
1	10	0.143
2	20	0.241
3	30	0.357
4	40	0.468
5	50	0.61
6	60	0.717
7	70	0.832

Table 2: Formulation of Paroxetine solid dispersions

Formulation code	Paroxetine: PEG 4000
A1	1:2
A2	1:2

Table 3: *In-vitro* drug release data of solid dispersions of Paroxetine: PEG4000

Time (in mins.)	A1 (Paroxetine:PEG4000) **(120:240)** **% of drug release**	A2 (Paroxetine: PEG 4000) **(120:240)** **% of drug release**
15	48.69	57.92
30	68.26	71.36
45	77.54	85.27
60	85.27	94.55

Table 4: Formulation of Paroxetine buccal films

Formulation	Polymer and its composition (mg)				Plasticizer (mL)	Sodium saccharin (mg)	Vanillin (mg)	D.water(mL)
	Paroxetine:PEG 4000	HPMC E 15	PVA	PVP				
F1	120:240	400			0.1	2	2	10
F2	120: 240	450			0.1	2	2	10
F3	120:240	500			0.1	2	2	10
F4	120:240		400		0.1	2	2	10

F5	120:240		450		0.1	2	2	10
F6	120:240		500		0.1	2	2	10
F7	120:240	300		100	0.1	2	2	10
F8	120:240	350		100	0.1	2	2	10
F9	120:240	400		100	0.1	2	2	10

Table 5: Evaluation data for mucoadhesive buccal films

Formulation Code	Weight variation(mg)	Thickness(mm)	Folding endurance	% Drug content	Disintegration time (sec)
F1	46.21±0.67	0.15 ± 0.012	344.67 ± 4.64	91.77434457	34.67 ± 1.25
F2	47.83±0.36	0.17 ± 0.012	321.00 ± 2.45	95.61329588	37.33 ± 1.70
F3	49.95±0.43	0.17 ± 0.008	324.33 ± 2.49	92.89794007	46.67 ± 1.25
F4	51.65±0.50	0.21 ± 0.008	344.33 ± 2.05	93.27247191	34.00 ± 2.16
F5	50.96±0.56	0.23 ± 0.008	338.33 ± 1.25	91.77434457	38.67 ± 2.62
F6	52.05±0.009	0.21 ± 0.012	353.00 ± 3.74	97.43913858	32.67 ± 1.70
F7	48.06±0.21	0.18 ± 0.008	323.67 ± 2.49	95.75374532	42.67 ± 2.05
F8	51.85±1.25	0.18 ± 0.012	316.67 ± 2.62	96.9241573	47.33 ± 1.70
F9	50.31±0.77	0.19 ± 0.012	330.67 ± 1.25	96.9241573	41.67 ± 1.70

Table 6: *In-vitro* release data of buccal films of formulation F1 to F9

Formulation Code	F1	F2	F3	F4	F5	F6	F7	F8	F9
2 m	45.92	42.92	50.92	38.00	41.92	35.00	26.00	21.00	23.00
4 m	64.24	58.21	66.25	51.18	57.21	50.17	31.16	26.13	29.15
6m	73.29	70.27	76.30	59.22	66.25	57.21	40.12	36.18	35.18
8m	81.33	83.34	83.34	66.25	72.28	68.26	53.19	43.14	46.15
10m	86.35	88.36	91.38	75.30	82.33	76.30	63.24	51.18	55.20
12m	92.38	93.39	97.41	82.33	87.36	84.34	70.27	63.24	66.25
14m				89.37	93.39	87.36	78.31	71.28	75.30
16m				94.39		91.38	84.34	79.32	83.34
18m							90.37	86.35	88.36
20m								91.38	93.39

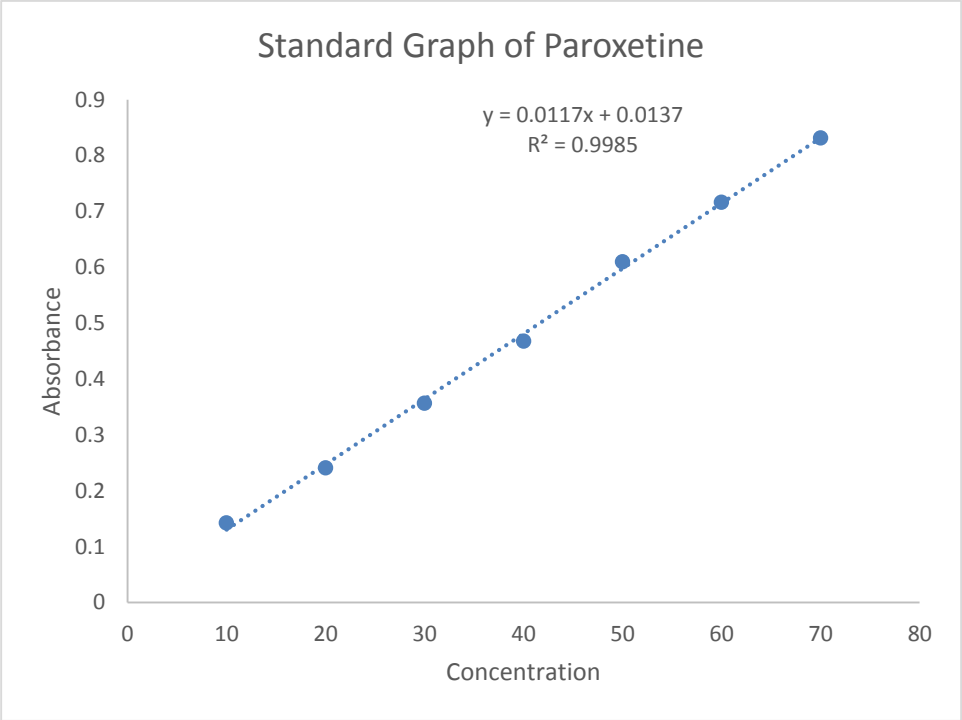

Figure 1: The standard graph of Paroxetine using simulated saliva buffer of pH 6.8

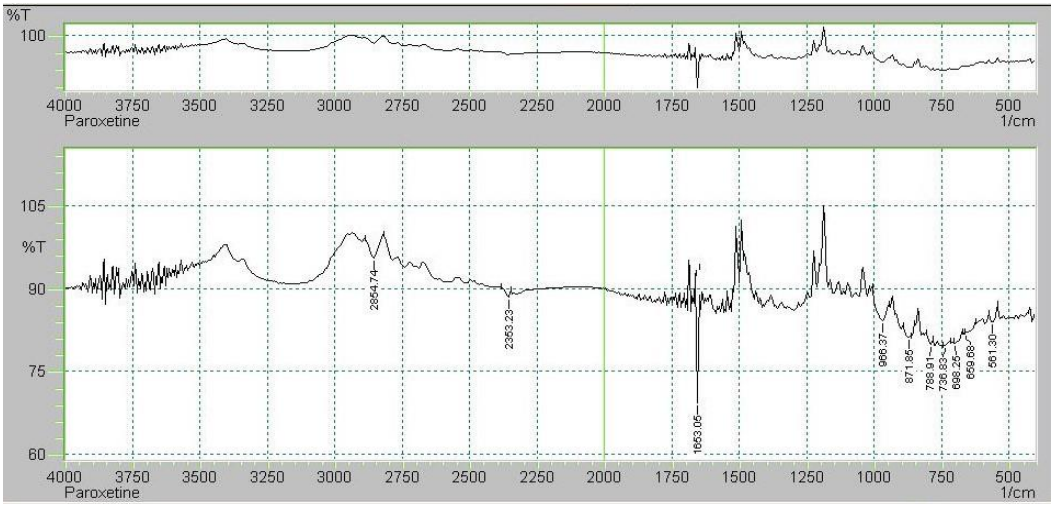

Figure 2: FTIR Spectrum of pure drug (Paroxetine)

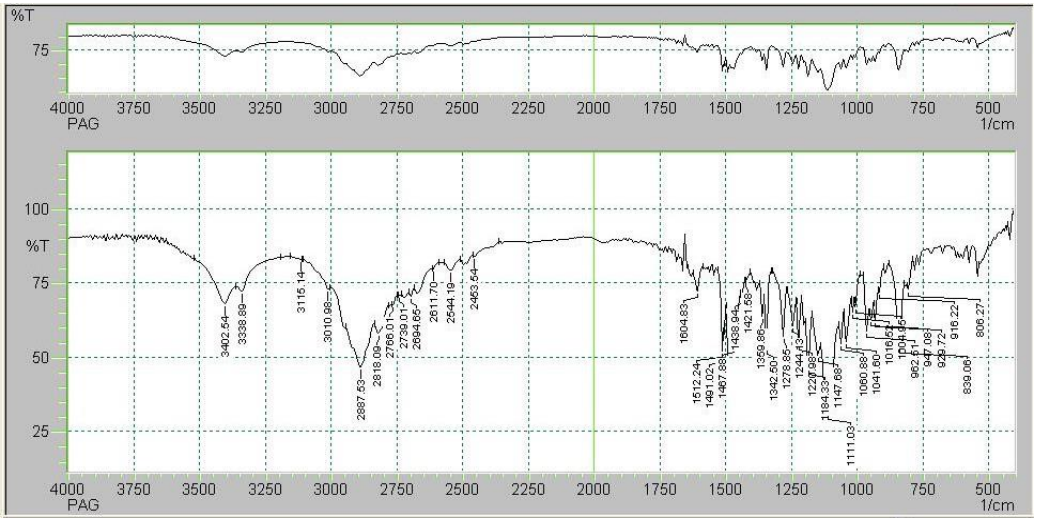

Figure 3: FTIR Spectrum of Paroxetine+ PEG 4000

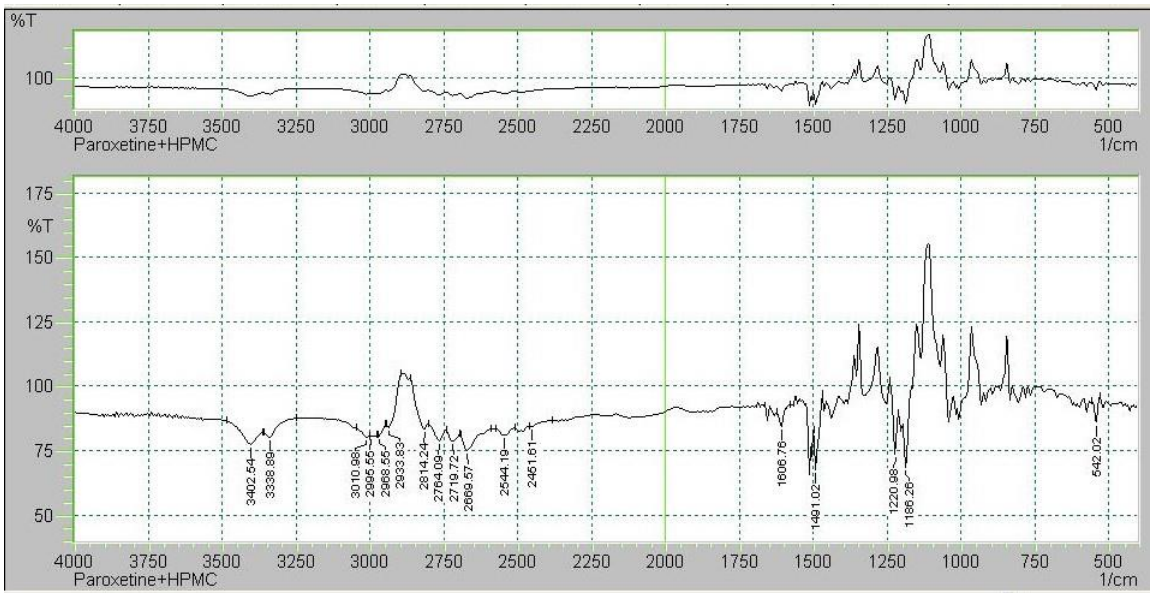

Figure: 4: FTIR Spectrum of Paroxetine+ HPMC

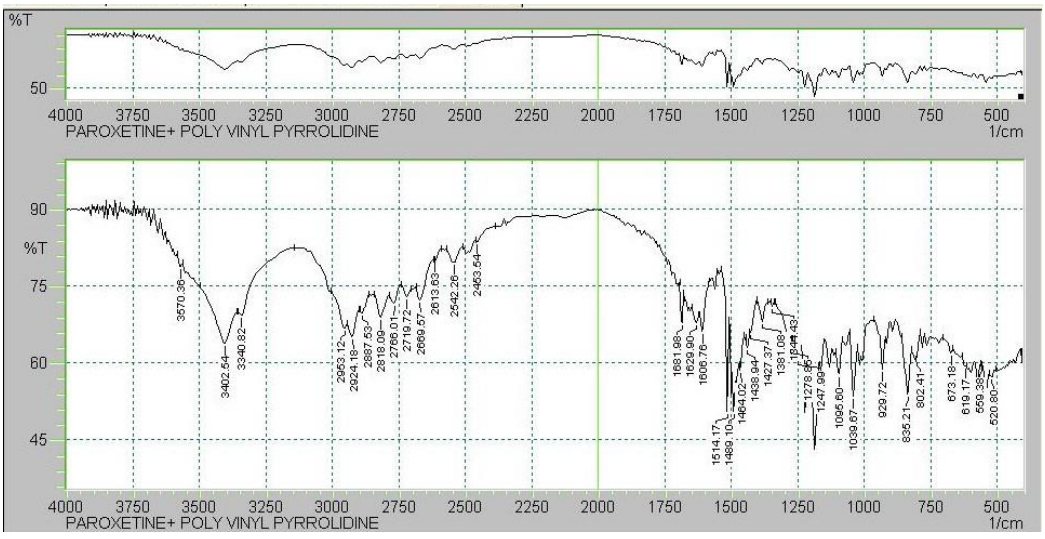

Figure 5: FTIR Spectrum of Paroxetine+ PVP

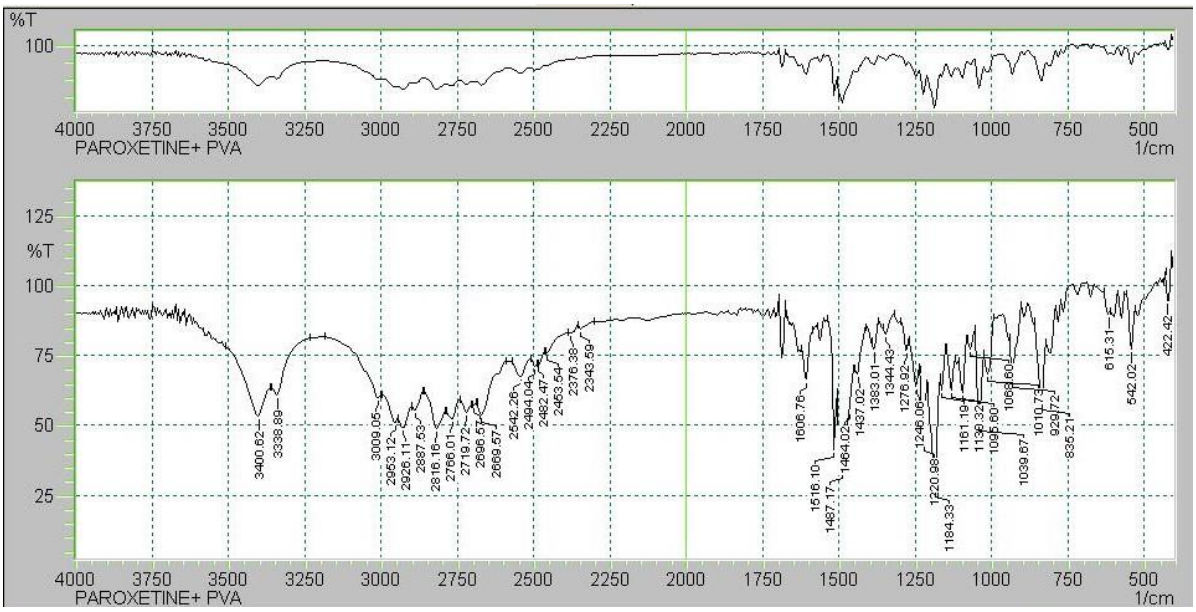

Figure 6: FTIR Spectrum of Paroxetine+ PVA

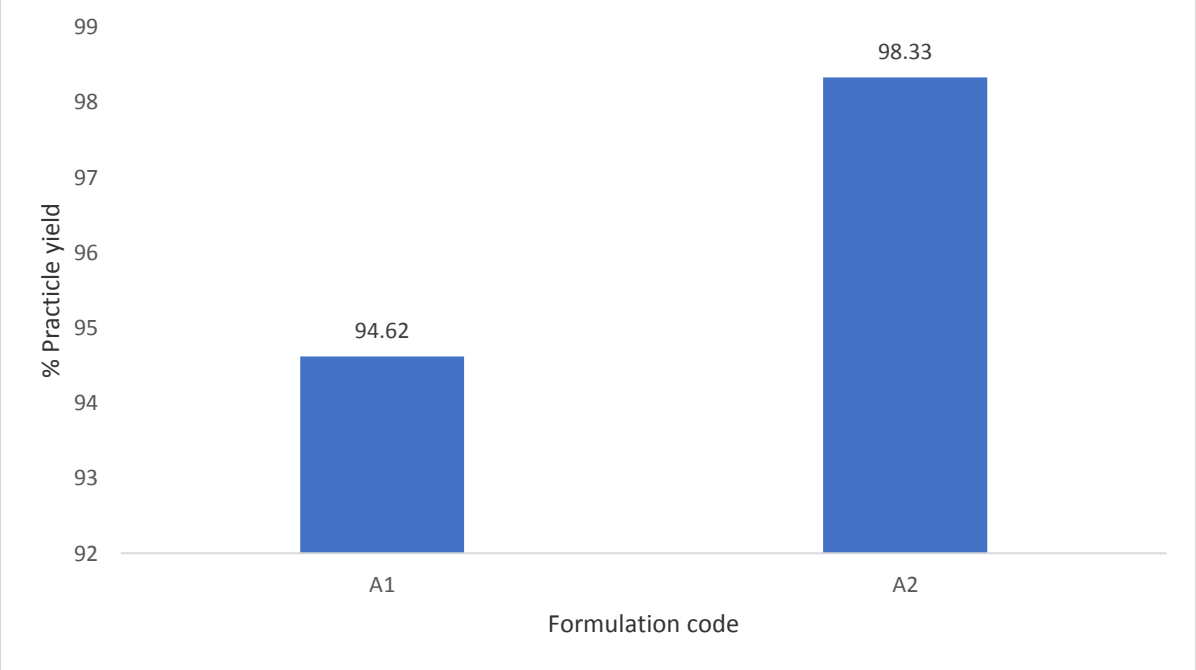

Figure 7: % Practical yield of solid dispersions

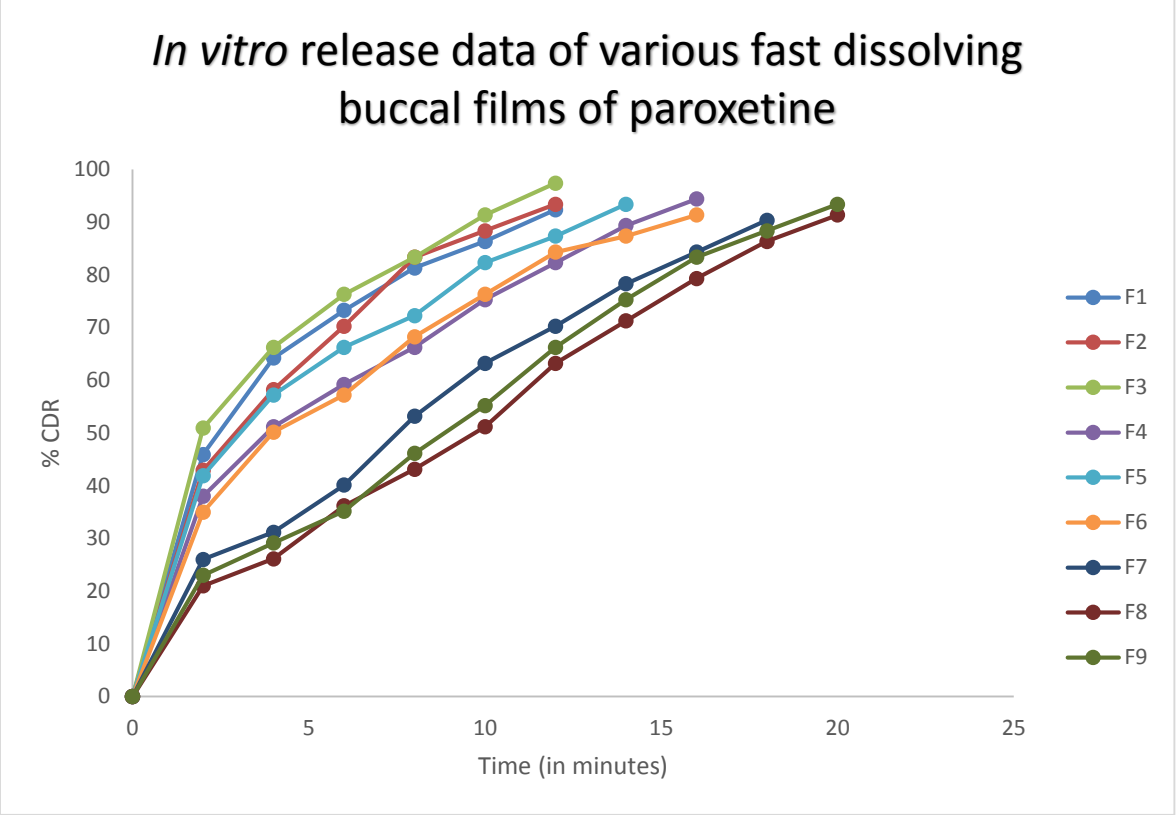

Figure 8: *In vitro* drug release profile of formulations F1-F9

CONCLUSION:

All the formulation showed acceptable quality control property formulation F3 having polymer concentration HPMC E 15 showed better % of drug release rate at the end of 12minutes, thus formulation F3 was found to be the most promising formulation on the basis of acceptable evaluation property and the *In-vitro* drug release rate of 97.41%. Based on the FTIR studies appear to be no possibility of interaction between the Paroxetine and polymers of other excipients used in the films. Stability studies were conducted for the optimized formulation as per ICH guidelines for a period of 90 days which revealed that the formulation was stable. The result suggests that the developed mucoadhesive buccal film of Paroxetine could perform the better than conventional dosage form leading to improved efficacy and better patient compliance.

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