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Formulation and evaluation of oral disintegration strips

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Abstract
Over the recent past, many of the research groups are focusing their research on this technology. Amongst Oral drug delivery system Oral Strip Technology (OST) is gaining much attention. The advantages of OST are the administration to pediatric and geriatric patient population where the difficulty of swallowing larger oral dosage forms is eliminated. This technology has been used for local action, rapid release products and for buccoadhesive systems that are retained in the oral cavity to release drug in controlled fashion. OST offers analternate platform for molecules that undergo first pass metabolism and for delivery of peptides. An ideal OST should have the following properties: high stability, transportability, ease of handling and administration, no special packaging material and/or processing requirements, no water necessary for application, and a pleasant taste. All these requirement are fulfilled by the oral films. The OST is a good tool for product life cycle management for increasing the patent life of existing molecules or products. Compared to some of the complicated and expensive process (like lyophilization) used to manufacture ODTs (Orally Disintegrating Tablets), the OST is relatively easy to fabricate, thus reducing the overall cost of the therapy. One of the reasons is that the buccal mucosa is less permeable and is thus notable to elicit a rapid onset of absorption and hence better suited for formulations that are intended for sustained release action. Further, the buccal mucosa being relatively immobile mucosa and readily accessible, it makes it more advantageous for retentive systems used for oral trans mucosal drug delivery. The primary disadvantage associated with buccal delivery route is the low flux that in turn results in low drug bioavailability. To overcome this hurdle, various buccal penetration enhancers have been studied which improve the absorption pattern of the molecules. The article shows OST encompassing materials used in OST, method of preparation, evaluation, applications, commercial technologies and future Business prospects of this technology.

Keywords: fast dissolving oral film, solvent casting technique, quality by design, taste masking

1. Introduction
The oral route is one of the most preferred route of drug administration as it is more convenient, cost effective and ease of administration lead to high level of patient compliance. The oral route is problematic because of swallowing difficulty for pediatric and geriatric patient who have fear of choking. Patient convenience and compliance-oriented research has resulted in bringing our safer and newer drug delivery system. There is a growing demand for novel dosage forms to cater to the needs of the population. In order to assist or satisfy these patients, several fast disintegrating drug delivery system have been developed and marketed. However, such fast disintegrating solid preparation suffer from certain major drawbacks including fear of choking, swallowing, fragility and friability and requirement of specialized and expensive packaging (Slowson *et al.*,1985; Doheny *et al.*,1993). In order to overcome such drawbacks and safety the needs of the market, intraoral film has been developed. This quick disintegrating film can be provided in various packages convenient for use, especially for children and elders. Various bioadhesive mucosal dosage forms have been formulated which include adhesive tablets, gels, ointment, patches and more recently the use of polymeric films for buccal delivery, known as mouth disintegrating films.
Buccal film involves material such as strips forming polymers, plasticizers, active pharmaceutical ingredients, sweetening agent, saliva stimulating agent, flavoring agents, coloring agents, stabilizing and thickening agents, permeation enhancers, and super disintegrants.
A typical composition contains the following:

- Drug 1-25 %
- Film forming polymers 40-50 %
- Plasticizer 0-20 %
- Sweetening agent 3-6 %
- Saliva stimulating agent 2-6 %
- Flavoring agent 10 %
- Coloring agent 1 %

Experimental Work
Formulation of fast Dissolving Film.
Sildenafil Citrate fast dissolving films were prepared according to formula. Total sixty formulations were prepared.

Preparation of Blank Films
Polymers were accurately weighed and dissolved in respective solvent and then add PEG 400 as a Plastisizer and casted in a glass petridish using castor oil as a lubricant. The films were allowed to dry at a normal room temperature for 24 hr.

Process for preparation of fast dissolving Film by solvent casting method.

- Accurate amount of polymer was weighed and socked in respective solvents for overnight.
- Sildenafil citrate was dissolved in required quantity of solvent.

- The solution was mixed and PEG 400 was added as a plasticizer.
- The solution was heated and kept standing for half an hour for getting the proper viscosity. (The solution should be stirred continuously while heating).
- The solution was sonicated for 15 mins to remove the air bubbles.
- Then the solution was kept overnight and next day casting procedure was carried out.
- Next day, the solution was poured in petridish and left it overnight for proper drying.
- After complete drying of film, film was removed with the help of cutter.
- The film was wrapped with aluminum foil and store in normal room temperature

A. Formulation of Blank fast oral Dissolving Film.

Table 1: Composition of blank film

Ingredients	A	B	C	D	E	F	G	H	I	J
PEG 400 (ml)	1	1	1	1	1	1	0.5	0.4	0.5	1
HPMC E4(mg)	25	20	25	20	20	25	20	20	25	30
Mannitol (mg)	5	5	5	5	5	5	5	5	5	5
Glycerin (ml)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Crosscarmellose (mg)	5	5	10	10	10	10	5	10	10	10
Ethanol (ml)	2	2	2	2	1	1	2	2	2	2
Titanium Dioxide (mg)	1	1	1	1	1	1	1	1	1	1
Tween 80	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs
Menthol (mg)	10	10	10	10	10	10	10	10	10	10

B. Formulation for Fast Dissolving Oral Film of Sildenafil Citrate

Table 2: Composition of Sildenafil Citrate film

Ingredients	A	B	C	D	E	F	G	H	I	J
SLC (mg)	25	25	25	25	25	25	25	25	25	25
HPMC E4 C (mg)	25	20	25	20	20	25	20	20	25	30
PG (ml)	1	04	1	1	2	0.5	1	0.4	0.4	0.5
Mannitol (mg)	5	5	5	5	5	5	5	5	5	5
Glycerin (ml)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Crosscarmellose (mg)	5	5	10	10	10	10	5	10	10	10
Ethanol (ml)	2	2	2	2	1	1	2	2	2	2
Titanium Dioxide (mg)	1	1	1	1	1	1	1	1	1	1
Tween 90	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs
Menthol (mg)	10	10	10	10	10	10	10	10	10	10

Evaluation Parameter of Fast dissolving oral Film

- **Thickness**

The thickness of the film was measured using digital verniar caliper with a least count of 0.09 mm at different spots of the film. The thickness was measured at three different spots of the film and average was taken and Standard Deviation was calculated.

- **Weight Variation**

1.5 centimeter square (1 X 1.5 cm) of the film was cut at three different places from the casted film. The weight of each film was taken and weight variation was calculated.

- **Folding Endurance**

Folding endurance was determined by repeated folding of the film at the same place till the strip breaks. The number of times the film is folded without breaking was computed as the folding endurance value.

- **Surface pH**

The surface pH of fast dissolving film was determined in order to investigate the possibility of any side effect *in vivo*. As an acidic or alkaline pH may cause irritation of 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 film 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 procedure was performed in triplicate and average with standard deviation was reported.

- **Disintegration Time**

In vitro disintegration time was determined visually in a petridish containing 25 ml of pH 7.2 artificial saliva with swirling every 12 sec. The disintegration time is the time when the film starts to break or disintegrates.

- **Drug Content**

Drug content determination of the film was carried out by dissolving the film of 1.5 cm2 in 100 ml of pH 6.8 phosphate buffer using magnetic stirrer for 1 hour. The drug concentration was then evaluated spectrophotometrically at λmax of 292 nm. The determination was carried out in triplicate for all the formulations and average with standard deviation was recorded.

- ***In-vitro* Dissolution**

The dissolution study was carried out using USP Type I (Basket type) dissolution apparatus. The dissolution was carried out in 900 ml of 0.01N HCl maintained at 37°C at 50 rpm. 5 ml aliquots of samples were taken at various time intervals which were replaced with same volume of fresh 0.01 N HCl maintained at 37°C. Sildenafil Citrate in the samples was then determined spectrophotometrically at λmax of 292 nm. The results were expressed as mean of three determinations.

- ***In vitro* permeability studies**

Franz diffusion cell is one of the most widely used systems for *in vitro* skin permeation studies. The cell consists of a small donor and receptor compartment which is stirred by Teflon coated magnetic bead. The drug delivery is by the vertical movement of drug from donor phase through the skin into the receptor phase. Membrane was mounted facing the donor compartment. The available diffusion area between cells was 4 cm2. In the donor compartment, the formulation of film was placed in intimate contact with the membrane. The receptor compartment was filled with phosphate buffer pH 6.8 kept at constant temperature of 37 ±0.50C and stirred by a magnetic stirrer. The top of the donor compartment was covered with aluminum foil. At appropriate intervals (1, 2, 3, 4, 5, 6, 7, 8 hr), 4 ml aliquots of the receptor medium were withdrawn and immediately replaced by an equal volume of fresh receptor solution. Samples were analyzed spectrophotometrically at 292nm.

Stability Studies

The purpose of the stability testing is to provide evidence on how the quality of drug substance or drug product varies with time under the influence of a variety of environment factors such a temperature, humidity and light, enabiling recommended storage condition re-test periods and shelf life. The stability studies were carried out as per Internationational conference of harmonization (ICH) Guidelines stability studies were carried out of 400C / 75% RH for 1months. The optimized film formulations were packed in amber - colored bottles, which were tightly plugged with cotton and capped. They were then stored at 400C / 75% RH for1 months and evaluated for their

physical apperance, drug content and in-vitro dispersion time of specified intervals of time.

Result and Discussion

Preformulation Study

Physical Characterization of Sildenafil Citrate

Table 3: Physical characterization of sildenafil citrate

Experimental	Property Studied	Result
Organoleptic Property	Colour	White
	Odour	Odourless
	Taste	Slightly Bitter
	Nature	Hygroscopic
Identification of drug	Melting Point	186-188^{0}C
Characterization of Powder.	Angle of Repose	250.71'θ
	Bulk Density	0.574 gm / cm^1
	Tapped Density	0.765 gm/ml
	Carr's Index	24.96%
	Hausner's Ratio	1.33 %

Analytical Characterization of Sildenafil Citrate

A. Infrared absorption spectrophotometry

All prominent and primary peaks were observed in FTIR spectrum of sildenafil citrate.

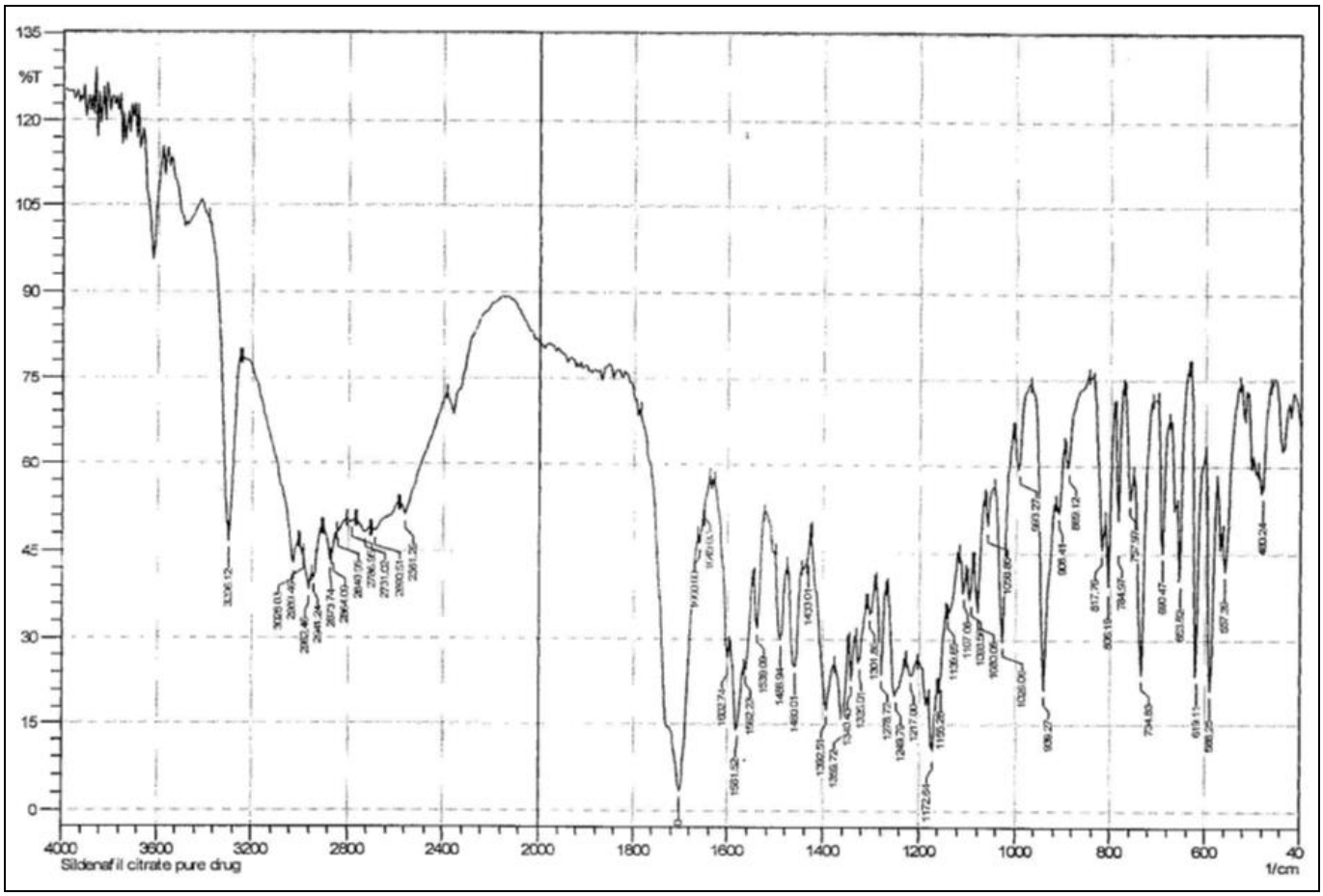

Fig 1: FTIR Spectrum of Sildenafil Citrate

Above Figure shows various peaks of a drug of various position in IR spectra. The structure of the drug consist of aromatic ring C-H group at 3296.12 cm -1, aliphatic ring C-H group at 2941.24 cm -1, a peak at 2561.25 cm -1 O -H group, a peak at 1750 cm -1 C=O group, a peak at 1340.43 cm-1 C-N group, a peak at 1392.51 cm -1S=O group.

Drug excipient compatibility study

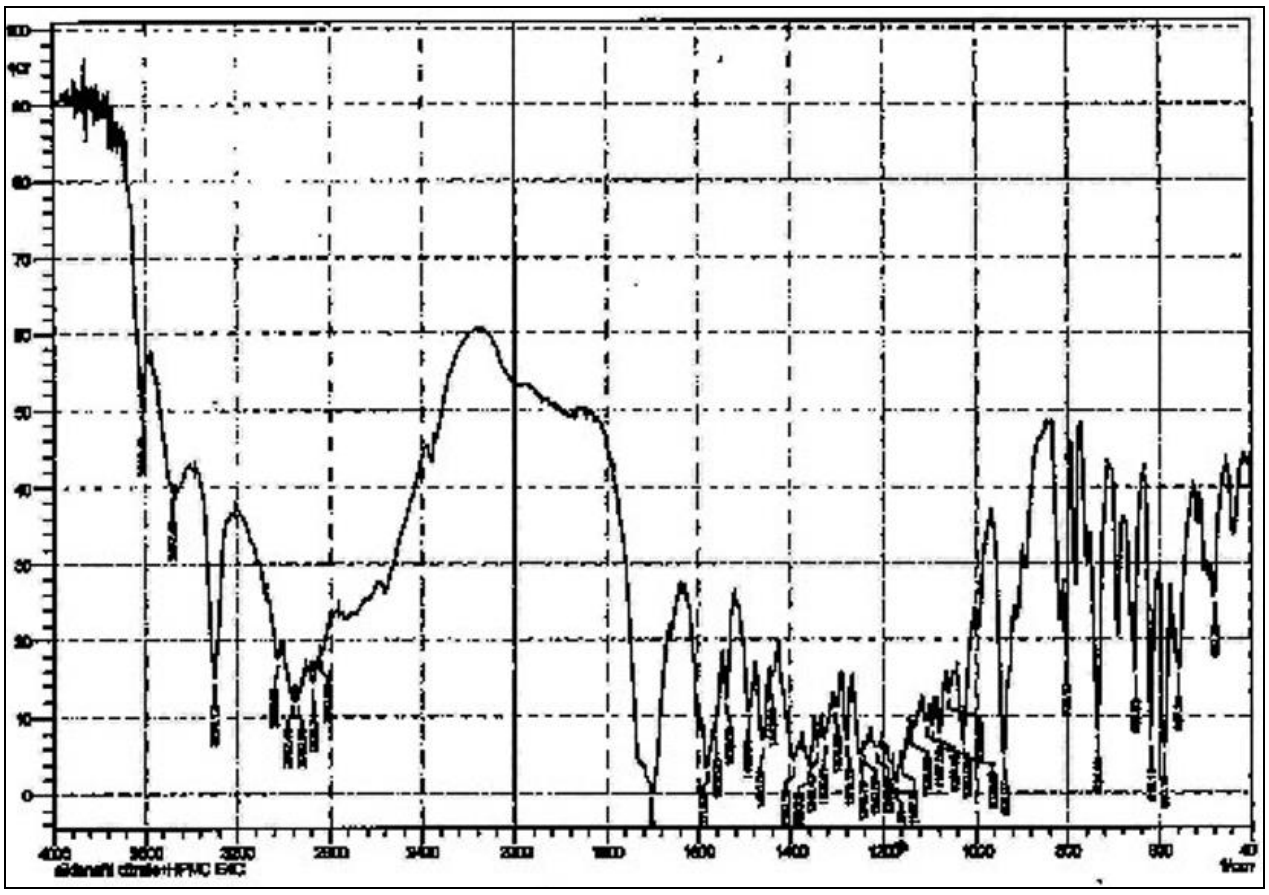

Fig 2: FTIR spectrum of sildenafil citrate with HPMC E4 C.

Above figure shows various peaks of drug and polymer at various position in IR spectra.

The structure of the drug consist of aromatic ring C-H group at 3296.12 cm-1, A peak 3477.42 cm-1 N-H group, a peak at 3610.49 cm -1 O-H group, a peak at 2840.95 cm CH3 group

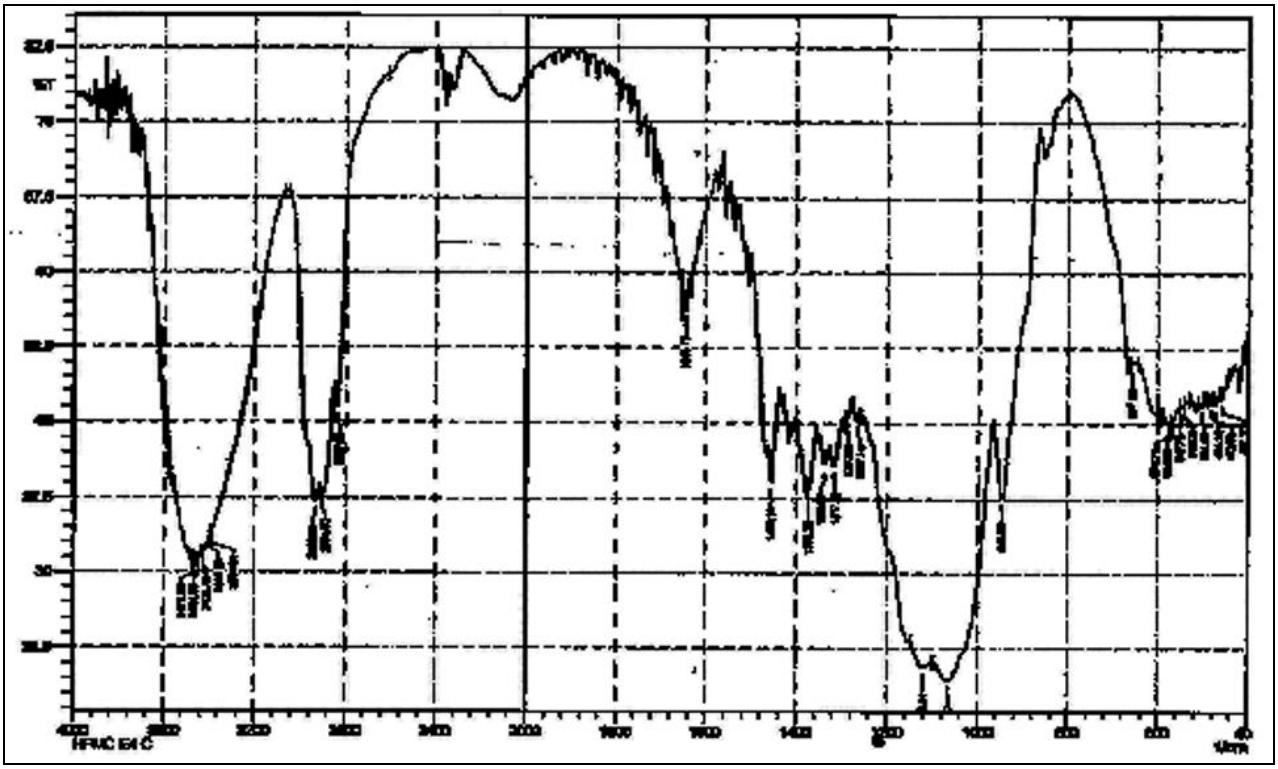

Fig 3: FTIR spectrum of HPMC E4 C.

Above figure shows various peak of polymer at various position in IR spectra. The structure of polymer consist of O -H group at 3471.83 cm -1. a peak at 2933.53cm-1C-H group, a peak at 2637.09 cm -1 carboxyl acid group.

Table 4: Details of FTIR study

Sr. No.	Funtional Group	Peaks observed in Sildenafil citrate	Peaks observed in HPMC E4C	Peaks observed in mixture of sildenafil citrate and HPMC E4C
1	Aromatic C-H	3296.12	-	3296.12
2	Aliphatic C-H	2941.24	2933.53	-
3	O-H group	2561.25	2471.83	3610.49
4	C=0 group	1760	1845.17	-
5	C-N group	1340.49	1373.22	-
6	S=O Group	1392.51	-	-
7	Carboxyl acid group	-	2637.09	-
8	N-H group	-	-	2477.42
9	CH_3	-	-	2840.95

Drug and Excipents Interaction study:
Above table shows various peaks of drug at various position in IR spectra. The structure of the drug consist of aromatic ring C-H group at 3296.12 cm-1aliphatic C-H group at 2941.24 cm-1, The polymer HPMC E4C shows peaks for OH group at 3471.83 cm-1aliphatic C-H at 2933.53 cm-1 and peaks for C=O at 1845.17 cm-1. All the peaks were retained in the mixture of drug and polymer. Hence it can be concluded that there is no interaction between drug and polymer.

Standard calibration curve of sildenafil citrate
Standard calibration curve of sildenafil citrate
The standard calibration curve for sildenafil citrate was prepared for concentration of 0.1µg/ml to 0.5µg/ml at 292 nm. The graph absorbance v/s concentration was plotted and data was subjected to linear regression analysis. The data of absorbance is as shown in Table

Table 5: Calibration data of sildenafil citrate in 0.01N HCL

Sr No.	Concentration (ug/ml)	Absorbance
1	0	0.000
2	0.1	0.247
3	0.2	0.350
4	0.3	0.467
5	0.4	0.561
6	0.5	0.692

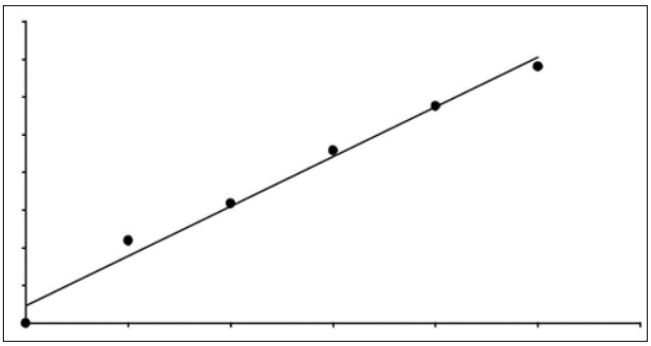

Fig 4: Standard Calibration curve of sildenafil citrate in 0.01N HCL

Correlation Coefficient (R) = 0.9923
Equation for regressed line; Y= 14.93x + 0.604
Where,
X= value for concentration,
Y = regressed value of absorbance
14.93 = slope of regressed line

Calibration curve for Sildenafil citrate in phosphate buffer 6.8 in the concentration 0.1 µg/ml to 0.5 µg/ ml was straight line. The absorbance increased with increase in concentration, thus the standard curve follow the Beer-Lambert's Law.

Standard calibration curve of sildenafil citrate
The standard calibration curve For sildenafil citrate was prepare for concentration of 0.1µg/ml to 0.5µg/ml at 292nm.The graph absorbance v/s concentration was plotted and data was subjected to linear regression analysis. The data of absorbance is as shown in Table.

Table 6: Calibration data of sildenafil citrate in phosphate buffer 6.8

Sr. No.	Concentration (ug /ml)	Absorbamce
1	0	0.000
2	0.1	0.145
3	0.2	0.243
4	0.3	0.400
5	0.4	0.518
6	0.5	0.652

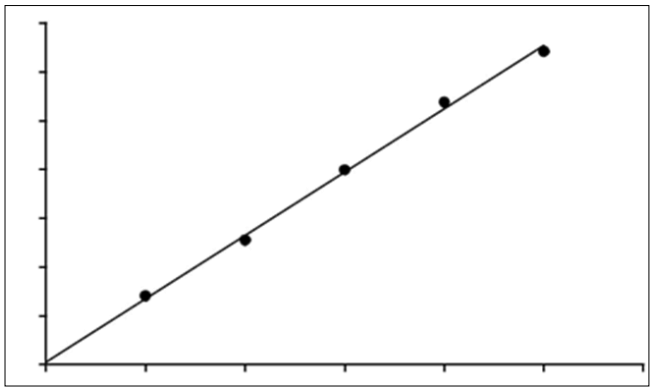

Fig 5: standard calibration of sildenafil citrate in phosphate buffer 6.8

Correlation Coefficient (R) = 0.9991
Equation for regressed line; Y= 15.37x + 0.061
Where,
X= value for concentration,

Y = regressed value of absorbance
15.37 = slope of regressed line

Calibration curve for Sildenafil Citrate in phosphate buffer 6.8 in the concentration 0.1µg/ml to 0.5µg/ ml was straight line. The absorbance increased with increases in concentration, thus the standard curve follow the Beer-Lambert's Law.

Evaluation of fast dissolving film.
Fast dissolving film were prepared in batches A to J and evaluated for film properties like

- Thickness
- Weight variation
- Folding endurance.
- Surface PH.
- Disintegration test.
- Uniformity of drug content.
- In-vitro dissolution studies.
- Ex-vivo permeation study.

Table 7: Evaluation of Sildenafil Citrate Film

Foundation Code	Thickness (mm)	Surface PH	Folding Endurance No. of Folds	Disintengration time (sec)	Weight (mg)
A	0.15	6.18	35	15	24.13
B	0.13	6.21	37	10	27.15
C	0.10	6.27	42	17	28.19
D	0.11	6.28	46	10	24.89
E	0.15	6.33	52	14	26.08
F	0.09	6.41	69	08	23.57
G	0.12	6.44	66	12	29.67
H	0.17	6.46	68	18	22.78
I	0.16	6.50	53	15	23.72
J	0.17	6.52	59	20	26.08

- **Thickness**

As all the formulations contain different amount of polymers, hence the thickness gradually varies with the amount of polymers. All the film formulations were found to have thickness in the range of 0.20 mm to 0.45 mm. The results are given in the table.

- **Surface pH**

The surface pH of the films was ranging from 6.18 to 6.52 as shown in table since the surface pH of the films was found to be around the neutral pH, there will not be any kind of irritation to the mucosal lining of the oral cavity.

- **Folding Endurance**

Folding endurance varies with the variation in the concentration of polymer. The number of time the film fold until it broke is reported. The film **F—J** passes the test.

- **Disintegration Time**

It was observed that disintegration time varies from 1 to 25 sec for all the formulations. Disintegration time of film containing HPMC E4 C as polymer was found to be Fast Dissolving Film i.e.5 min and 4 min.

- **Weight Variation**

1.5 centimeter square (1 X 1.5 cm) of the film was cut at three different places from the casted film. The weight of each film was taken and weight variation was found in the range of 23.57 which passes the test.

Table 8: Drug Content

Formulation Code	% Drug Release
A	72.84
B	75.90
C	82.32
D	88.22
E	91.93
F	93.12
G	96.19
H	97.80
I	98.04
J	98.30

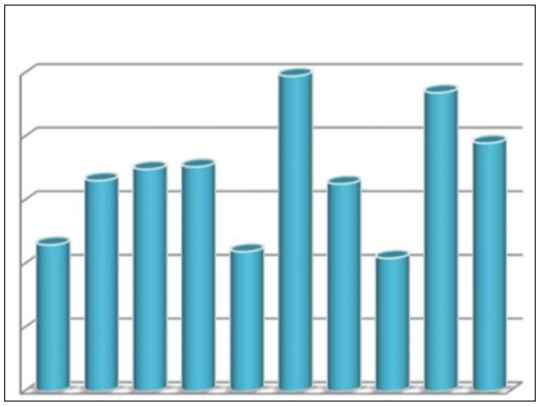

Fig 6: % Drug content

Drug Content
Drug content determination of the film was carried out by dissolving the film of 1.5 cm2 in 100 ml of pH 6.8 phosphate buffer using magnetic stirrer for 1 hour. The drug concentration was then evaluated spectrophotometrically at λmax of 292 nm. The drug content of the film was found to be in the range of 85% - 100%.

Table 9: % Cumulative Drug Release

Time (Min)	% Cumulative Drug ReleasE									
	A	B	C	D	E	F	G	H	I	J
0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
5	31.58	7.66	1.89	2.48	25.13	61.15	21.91	31.04	72.85	46.10
10	25.75	6.66	1.99	2.56	31.59	99.85	25.11	33.27	66.93	53.60
15	25.61	10.78	2.39	2.78	30.87	63.14	45.00	34.98	62.56	62.25
20	32.27	17.34	11.77	3.03	34.70	58.08	40.12	32.40	61.65	68.30
30	29.93	13.77	3.14	3.92	51.73	68.75	39.21	41.35	54.57	27.46
45	32.14	17.14	3.60	2.89	44.23	75.13	35.87	32.12	47.90	38.77
60	34.90	15.18	3.42	3.83	183.1	83.45	51.30	35.68	46.25	35.69

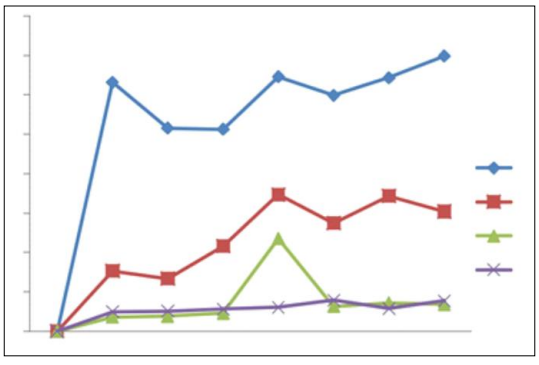

Fig 7: % cumulative drug release A-D

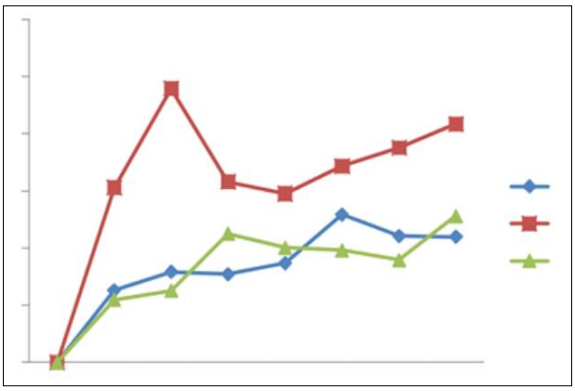

Fig 8: % cumulative drug release E-G

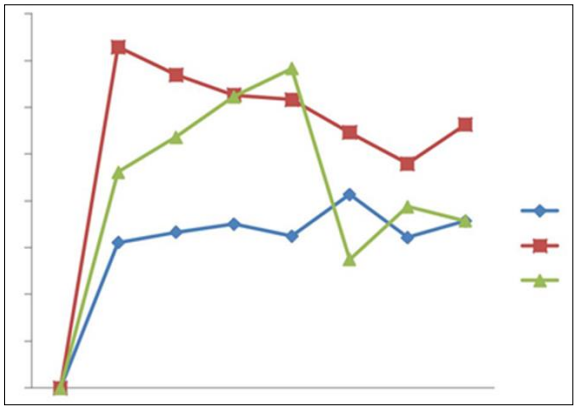

Fig 9: % cumulative drug release H-J

In-vitro Dissolution

In vitro drug release profiles of the formulations in pH 6.8 phosphate buffer show differences depending on their composition as given in table. A rapid dissolution of all the film preparations was observed by the dissolution test, in which approximately 95% of sildenafil citrate was dissolve within 10 min. It was also observed that HPMC E4C was able to modulate the sildenafil citrate release as lower amount of HPMC E4C resulted in release of drug at faster rate

Table 10: *In-Vitro* Permeability Studies

Time (MTh)	% Drug Release	
	F	I
0	00	00
5	80.96	79.0
10	99.23	80.24
15	67.99	66.90
20	51.82	48.37
25	25.94	27.06
30	12.6	6.6

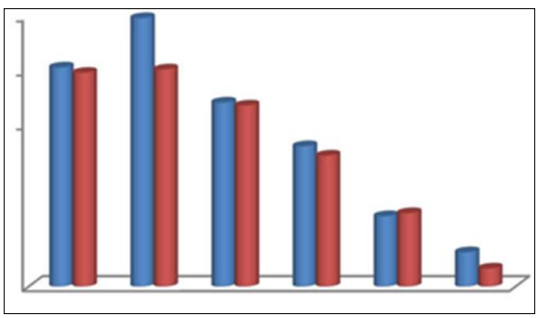

Fig 10: 19% cummulative drug permeated

In vitro ipermeability studies

The diffusion study for the formulated batch was carried out and it was found that the sildenafil film F with polymer HPMC E4C gave release of 99% in 10 mins where as, the sildenafil film F with polymer HPMC K4 gave released of 80 % in 10 mins.

Stability Studies

The promising formulations were subjected to short therm stability studies. The formulation F were selected and stored at 400C/75% RH and tested for one month. The films were agian analyzed for the surface PH, durg content uniformity and disintegration time. The increase in the disintegration time was found to be within the permissible limits and the results were shown in the table.

Table 11: Stability Study Data

Formulation	Month	Disintegration time	Surface pH	Drug Content (%)
F	1 Month	14	6.41	93.12

Optimization of Formula

From the above study, it was found that the formulation containing HPMC E 4 C shows good drug release as compared with the formulation. The formulation F containing 100 mg HPMC E 4 C has shown 99 % drug release in 10 min. The thickness and weight variation of the film 'F' was found to be 0.09 mm and 0.18 which was in range. The pH of the film 'F' was found to be 6.41 i.e neutral pH which will not show any kind of irritation to the oral cavity Folding endurance was found to be more than 169. The disintegration time was found to be 12 sec.

Summary and Conclusion

The most popular solid dosage forms are being tablet and capsule; one important drawback of these dosage form for some patient, is difficult to swallow. Drinking water plays important role in swallowing of oral dosage form. For these reason films that can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention. Oral fast dissolving film are not only indicated for the people who have swallowing difficulties, but also are ideal for active people. Fast dissolving film are those when put on oral mucosa, disintegrate instantaneously releasing the drug which dissolve or disperse in saliva.

In the work undertaken an attempt was made to explore the use of film forming polymer in the formulation of fast dissolving films of sildenafil citrate and sucrose as a sweetner to mask the slight bitter taste of sildenafil citrate.

The concept of formulating fast dissolving film containing sildenafil citrate offers a suitable and practical approach in serving the desired objective of faster disintegration and dissolution characteristic.

In the present work fast dissolving films of sildenafil citrate was prepared by solvent casting method by using HPMC E4 C as polymer and propylene glycol as a plasticizers. Sweetner is used to mask the slight bitter taste of Sildenafil citrate. The purpose was to enhance patient compliances.

All films of sildenafil citrate were subjected to weight variation, thickness, surface pH, folding endurance, disintegration time drug content, and *in vitro* drug release.

Based on above studies following conclusion can be drawn:

- Evaluation parameter like weight variation, thickness, surface pH, folding endurance, disintegration time, drug

content, and *in vitro* drug release was within the acceptable limit.

- IR spectroscopic studies indicate that the drug was compatible with the excipient used.
- Based on the disintegration time, formulation F were found to be promising with disintegration time 4 sec. and showed the thickness in range 0f 0.25.
- The drug content of fast dissolving film of sildenafil citrate of formulation F was found to be 99.80 %
- The *in vitro* drug release from fast dissolving film of sildenafil citrate of formulation F was found 99.85% in 10 minute.

So it can be concluded that formulation F have showed the improved organoleptic performance and better patient compliance. This study showed an urgent need for new dosage form which can improve the patient compliance. For better taste masking effective technique is being developed constantly in the pharmaceutical industry. Presently the use of this technique depends upon the nature of the drug, thus the use of sweetner offers good taste masking of sildenafil citrate and its formulation into fast dissolving film offers advantage over conventional tablet.

References

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