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Design and evaluation of fast dissolving buccal films containing tadalafil

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ABSTRACT

The present research deals with formulation of a buccal film forming polymers based fast dissolving formulation of an erectile dysfunction drug, Tadalafil. This can offer higher patient compliance and excellent effectiveness of the drug. Low viscosity grade of hydroxypropyl methylcellulose (HPMC E 5 and HPMC E15) were used as excipient. Due to their excellent film forming property and palatable taste. PEG 400 and Propylene glycol were used as plasticizers. Tween 80 used as solubilizing agent, aspartame and menthol, pineapple flavor used as sweetener and taste masking agent respectively. Higher concentration of HPMC E 15 was resulted in sticky film formation. Concentration of PEG 400 and propylene glycol was optimized during preliminary studies. Formulation containing HPMC E 5 (150 mg), E 15 (100 mg) and PEG 400 and Propylene glycol (20 % w/w) showed optimum performance against all other prepared formulations. The formulation was found to show a significant improvement in terms of the drug release as compared to tablet formulation. Thus, fast dissolving buccal film formulation of Tadalafil was successfully developed.

Keywords: Fast dissolving buccal film, Tadalafil, Propylene glycol, Aspartame.

INTRODUCTION

Recently, fast dissolving drug delivery have started gaining popularity and acceptance as new drug delivery systems, because they are easy to administered and lead to better patient compliance. These delivery systems either dissolved or disintegrate in the mouth rapidly, without requiring any water to aid in swallowing. [1]. Oral dissolving drug delivery systems are in the form of solid tablets and designed to dissolve/disintegrate in the patient's mouth without the need to drink or chew. However, the fear of taking solid tablets and the risk of choking for certain patient populations still exist despite their short disintegration/dissolution times. Hence oral film drug delivery is a better alternative in such cases. [2]

The fast dissolving oral film preparation is a new drug delivery technique to provide medicines to patients with obstacles in swallowing. [3] This novel drug delivery system can also be beneficial for meeting the current needs of the industry are improved solubility/ stability, biological half life and bioavailability enhancement of the drugs. [4]

Fast dissolving films fulfill all the aforementioned requirements of potential solid oral dosage form for local delivery of Tadalafil. Fast dissolving film when placed in the oral cavity quickly gets hydrated, sticks onto the site of

application and then disintegrates to release the drug [4]. Thus, a fast dissolving film is a unique solid oral dosage form and has valuable advantages [6].

FDFs are prepared using fast disintegrating polymers that possess good film-forming properties e.g., hydroxypropyl methylcellulose [HPMC]. HPMC E LV is a low-viscosity white to off-white modified cellulose powder that is a good solubilizer and possesses swelling characteristics. Various grades of HPMC E LV (i.e., E5, and E15) were selected for this study. Solvent casting, semisolid casting, hot melt extrusion, solid dispersion extrusion, and rolling are processes used to manufacture FDFs. Solvent casting is the most common and traditional method. FDFs are typically evaluated for thickness, mechanical properties such as tensile strength and elasticity, *in vitro* and *in vivo* disintegration, and *in vitro* dissolution [7-8].

The interest in novel route of drugs administration occurs from their ability to enhance the bioavailability of the drugs impaired by narrow absorption windows in the gastrointestinal tracts. Drug delivery via the buccal routes using fast dissolving dosage forms offers such a novel route of drug administration. This route has been used successfully for the systemic delivery of drugs. [9]

Tadalafil is a phosphodiesterase 5 inhibitor used for the treatment of the erectile dysfunction. (ED). Water insoluble drug, the bioavailability of Tadalafil is about 28% by oral route. Half life is 17 hours. It undergoes extensive hepatic biotransformation. The main objectives of the present study were to prepare and evaluate the buccal dissolving thin film of Tadalafil and to study the various formulation variables that affect the drug release.

MATERIALS AND METHODS

Tadalafil was received as gift samples from Addis Ababa Pharmaceutical Factory, Ethiopia. HPMC E 5 and E 15 LV were received as generous gift sample from Adigrat Pharma Industry, Ethiopia. PEG-400, Propylene glycol, Aspartame, Menthol procured from S. D. Fine Chem. Ltd India based Ingredient LR-Grade, Tween 80 from Research lab Fine chem. India, Flavor Pine apple procured from Enrich Flavours, Adiss Ababa. All other ingredients and chemicals were analytical grade.

Method

Fast dissolving mouth film was prepared by using hydroxypropylmethyl cellulose (E5 and E15 LV) by casting method. The specified amount HPMC (E 5 and E 15 LV) polymer was weight and dissolved in 5 ml of water. Solution was kept aside for 10 min for swelling of polymer. Further required quantity aspartame was dissolved in 2 ml of hot water and specified quantity of menthol was dissolved in 1 ml of ethanol were added for the polymer solution under continuous stirring. 5 mg of drug was dispersed in polymer solution. Plasticizers (PEG-400 and Propylene glycol) pineapple flavor and poly-sorbate-80 were added to the solution. The solution was mixed using magnetic stirrer. The viscous solution was degassed under vacuum; the resulting bubbled free solution was poured onto glass mould (aluminum foil coated) of size 22.89 cm^2, which was place over a flat surface. The mould was kept for 12 hrs at room temperature for drying. The film was removed from the mould and preserved in butter paper and stored in desiccators [10]. Fast dissolving buccal films of Tadalafil were prepared by solvent casting method according to the formula given in Table-1. Various concentrations of HPMC-E-5 and E-15 were used to formulate the films all the batches containing different amount of polymers were evaluated further.

Table-1 Formulation of HPMC E5 and E15 LV films by casting method

Formula code	M1	M2	M3	M4	M5	M6	A1	A2	A3	A4	A5	A6
Tadalafil(mg)	29	29	29	29	29	29	29	29	29	29	29	29
HPMC E5 (mg)	200	150	200	150	150	150	-	-	-	-	-	-
HPMC E15 (mg)	-	-	-	-	-	-	100	120	100	120	100	100
Aspartame (mg)	2	2	2	2	2	2	2	2	2	2	2	2

PEG400 (%w/w)	20	20	-	-	20	-	20	30	-	-	20	-
P.G. (%w/w)	-	-	20	20	-	20	-	-	20	30	-	20
Pineapple Flavor mg	60	60	60	60	60	60	60	60	60	60	60	60
Menthol (% w/w)	10	-	-	10	-	-	10	-	-	10	-	-
Tween 80	-	-	-	-	10	10	-	-	-	-	10	10
D.W.(ml)	7	7	7	7	7	7	7	7	7	7	7	7

EVALUATION

Drug- Excipients Interaction studies

There is always a possibility of drug-excipients interaction in any formulation due to their intimate contact. The technique employed in this study is IR spectroscopy. IR spectroscopy is one of the most powerful analytical techniques which offer the possibility of chemical identification. The I.R. spectroscopy of Tadalafil was obtained by KBr pellet method and shown in Figure-1 & 2.

Drug Content: [10, 12, 13]

Drug content is determined by estimating the API content in individual strip. Limit of content is 85-115 percent [12]. Drug content was determined according to the following procedure. Three randomly selected films of size one square cm size from each batch were weighed accurately and dissolved in 2 ml of N, N-dimethyl formaamide and stirred continuously for 1 h on a magnetic stirrer. The volume was made up to 50 ml with phosphate buffer (pH 6.8) and then 1 ml was transferred to 10 ml volumetric flask and the volume was adjusted with phosphate buffer (pH 6.8). Solution was suitably sonicated and filtered. The absorbance was measured on a UV/Vis Spectrophotometer at 284 nm. The concentrations of Tadalafil were calculated (By correcting dilution factor) from a standard calibration curve of Tadalafil and the results are reported in Table-2

Thickness: [14]

The thickness of film is important for the brittleness of film. Thickness is dependent on the area of the Petri plate to be spread. The thickness of each film was measured at five different locations (center and four corners) using a micrometer screw gauge and a mean value of five locations was used as a film thickness (Generally it should be less than 200 µm).

Moisture loss study: [15-16]

The percent moisture loss studies were carried out to check the physical stability and integrity of the films. In the presence study the moisture loss capacity of the films was determined by placing the known weight and predetermined size (2x2) of films in dessicator containing anhydrous calcium chloride (inside the dessicator) for three days.

Moisture absorption study

Moisture absorption (MA) study was performed by a modified method of Kanig and goodman. Accurately weighed preconditioned films were placed in a constant humidity chamber (containing saturated solution of ammonium chloride which gives a relative humidity of 79.5%) set at room temperature. Films were weight at the interval of 1, 3 and 7 days.

Folding endurance: [5]

Folding Endurance of the 2x2 cm^2 films was determined by repeatedly folding at the same place till it broken. The number of times of patch could be folded at the same place without breaking gave the value of the folding endurance. This test was done on to individual films of each formulation batches.

In-vitro disintegration studies

Disintegration time gives an indication about the disintegration characteristic and dissolution characteristics of the film. The film as per the dimensions (2x2 cm^2) required for dose delivery was placed on a stainless steel wire mesh placed in a Petridis containing 10 ml distilled water. Time required for film to break was noted as in vitro disintegration time.

Mouth dissolving study: [17]

The mouth dissolving time was determined by placing the film manually into a beaker containing 50 ml of 6.8-pH phosphate buffer. Time required

by the film to dissolve was noted and the results are given in the table-3.

Palatability study: [18, 19]

Taste acceptability was measured by taste panel consisting of human volunteers (n=3) with 5 mg drug and subsequently 5 mg film sample held in the mouth for 5-10 s, then spat out and the bitterness level was recorded. Volunteers were asked to gargle with distilled water between the drug and sample administration. All the batches were evaluated for the palatability among the group of 3 volunteers. The mouth dissolving thin films were rated on the basis of taste, after bitterness and physical appearance. The following scale was used. + = very bitter, ++ = Moderate to bitter, +++ = slightly bitter, ++++ = Tasteless or taste masked.

In-vitro dissolution studies: [20-22]

The in vitro drug release of the films was determined using the USP XXIII apparatus type-2 (Shimadzu). The dissolution medium was 250 ml of phosphate buffer pH 6.8 the rotation speed was 50 rpm without the basket attached to it. The temperature of the dissolution media was maintained at 37º ± 05º C. During the study, 0.5 ml of aliquots was withdrawn at 4, 8, 12, 16 and 20, min and was replaced by fresh buffer. The aliquots were diluted at sufficient concentration with of phosphate buffer pH 6.8 and the amount of the drug release was analyzed spectrophotometrically at 284 nm. One film was placed into each vessel. The measurement was replicated five times with the standard deviation as a measure of variation.

Kinetic study

Model fitting of the release profiles using four different models viz. Zero order, first order, Higuchi matrix, Peppas model or Kor'smeyer equation.

Stability study: [23, 24]

Films of formula M2, M5 and A5 were stored at accelerated condition (65% relative humidity and 35ºC temperatures) for 45 days. Each film was wrapped in a butter paper followed by aluminium foil and placed in an aluminium pouch, which was heat sealed at the end. After 45 days the films were evaluated for appearance, weight, Tadalafil content, disintegration time, and in-vitro drug release and physical appearance observation after storage for 45 days and were compared for change in the dissolution profile.

RESULT AND DISSCUSSION

Drug- Excipients Interaction studies

FT-IR study was performed for the Tadalafil, HPMC E-5 and E-15 LV and physical mixture of all two. From the FT-IR spectra, the drug was found compatible with the polymers [Figure 1 & 2]

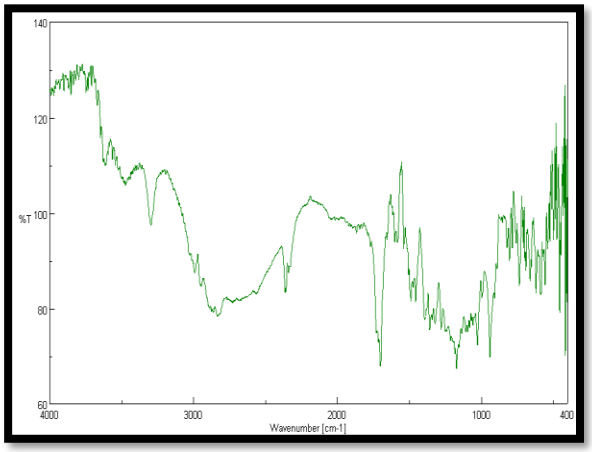

Figure. 1- FT-IR spectra of Tadalafil+ HPMC E-15

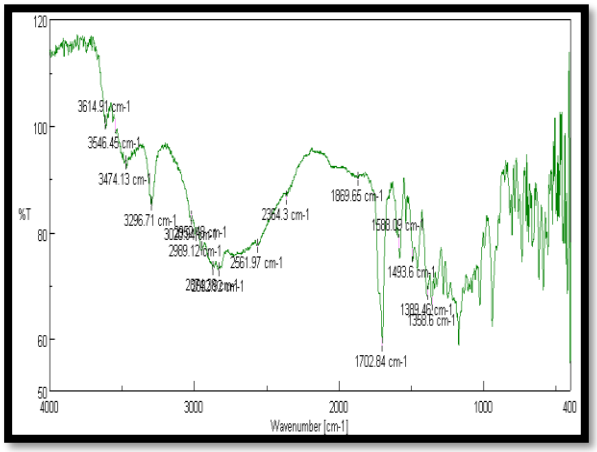

Figure. 2- FT-IR spectra of Tadalafil+ HPMC E-5

The preliminary trials were undertaken for designing the fast dissolving buccal films (FDBFs) were in the effect of casting surface and concentration of HPMC were assessed on the characteristics of the films. Batches containing various amount of HPMC E-5 and E-15 solution were casted on different surface which includes glass, plastic, petriplate wrapped with aluminium foil. Glass surface produced films with uneven surface. Separation could not be effectively

achieved when glass and plastics surfaces were adopted for film separation. aluminium foil surface exhibited complete film separation. It was concluded that casting surface significantly influenced the film formation and separation. Thus aluminum foil wrapped surface was selected as a casting surface for the formulation of FDBFs.

Drug content

Drug content was estimated for all the batches. The thin film was cut in 1 cm^2 area three randomly selected films from each batch and the cut parts were evaluated for drug content using UV Spectrophotometrically. All the batches were found satisfactory in drug content. All the films were found about in the range of standard. Result are depicted in Table no.-2

Thickness

All the batches were evaluated for thickness by using a micrometer screw gauge. As all the formulation contain different amount of polymers; hence the thickness was gradually increases with amount of polymers. All the batches were found to have thickness in the range of 0.05 mm to 0.07. Results are depicted in Table no.-2

Moisture loss study

All the batches were evaluated for % moisture loss Percent it has varies from 5.960 ± 0.351 to 9.800 ± 3.105. Out of all the prepared films, the formulation M6 of HPMC E 5 LV films showed lowest % moisture loss. This might be because of the high water permeability of HPMC polymer. The results were reported in the Table no.-2

Table 2 - evaluation results of the films

Sr.No.	Formcode	Drug content Mean ± STD*	Thickness Mean ± S.D*	% Moisture Loss Mean ± S.D*	%Moisture Absorption Mean ± S.D*	Folding Endurance Mean ± S.D*
1	M1	95.60 ± 4.21	0.070 ± 0.007	9.36 ± 0.967	9.100 ± 1.333	32 ± 3
2	M2	92.47 ± 5.59	0.070 ± 0.007	6.620 ± 0.729	6.127 ± 0.996	34 ± 4
3	M3	100.27 ± 8.73	0.060 ± 0.007	7.733 ± 0.955	9.597 ± 2.384	36.6 ± 3.2
4	M4	93.20 ± 1.83	0.070 ± 0.007	6.460 ± 41.10	7.183 ± 1.157	31 ± 2.6
5	M5	94.87 ± 4.73	0.064 ± 0.009	6.777 ± 2.353	8.110 ± 1.433	35 ± 3
6	M6	92.47 ± 4.76	0.058 ± 0.008	5.217 ± 1.266	6.150 ± 1.764	38.3 ± 2.08
7	A1	105 ± 3.67	0.052 ± 0.008	5.960 ± 0.351	7.363 ± 1.764	72.3 ± 4.93
8	A2	96 ± 2.50	0.070 ± 0.007	7.110 ± 1.494	8.340 ± 2.465	65 ± 3.61
9	A3	95.20 ± 3.17	0.050 ± 0.007	9.680 ± 1.222	8.417 ± 1.881	63.6 ± 5.13
10	A4	93.60 ± 3.67	0.052 ± 0.008	6.593 ± 3.235	9.717 ±3.334	64.3 ± 6.81
11	A5	95.93 ± 5.32	0.068 ± 0.008	9.800 ± 3.105	5.710 ± 2.075	66.3 ± 3.79
12	A6	95.93 ± 4.74	0.070 ± 0.007	9.230 ± 1.357	15.330 2.304	67.6 ± 4.16

* Standard deviation, n =3

Moisture absorption study

Percentage moisture absorption was measure manually moisture absorption varies from 5.710 ± 2.075 to 15.330 ± 2.304. The results were reported in the Table no.-2

Folding endurance: The folding endurance was measured manually for the prepared films. A film was repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gave the value of folding endurance. Figure- 3 shows the result for all the batches. Batches with lower amount of HPMC and lower viscosity grade of HPMC were found having folding endurance between 72.33 ± 4.93 to 67.67 ± 4.16. batches with higher amount of HPMC (E-15) scored lower folding endurance than the higher once. Batch A1 containing 1000 mg of HPMC (E-15) had scored highest folding endurance. Result are depicted in table no.-2

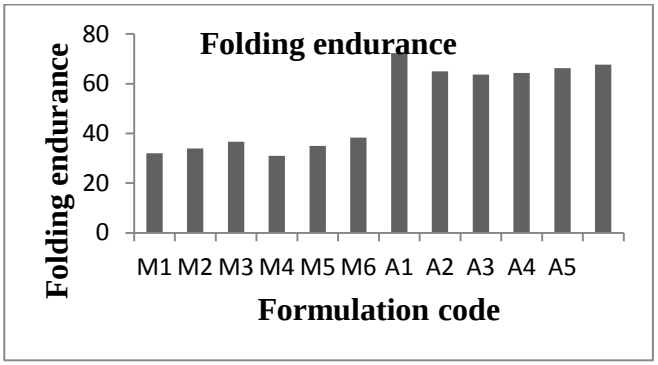

Figure 3- Comparison of folding endurance of buccal dissolving films

In-vitro disintegration time

Disintegration taste was performed for all the batches found to disintegrating within 34 seconds. Batches with high amount of polymers had comparatively high disintegration time as per Table no.-3

Table no. 3- evaluation results of films

Sr.No.	Form code	In-vitro disintegration time (sec) Mean ± S.D*	Mouth dissolving time (sec) Mean ± S.D
1	M1	42.67 ± 2.52	45.66 ± 3.51
2	M2	36.33 ± 3.06	39.33 ± 2.51
3	M3	37.33 ±1.53	44 ± 3.60
4	M4	41.67 ± 1.53	35 ± 2.64
5	M5	40.67 ± 3.51	41.66 ± 2.51
6	M6	42.33 ± 2.31	41.66 ± 0.57
7	A1	34.33 ± 2.08	36.33 ± 1.52
8	A2	36.33 ± 2.52	39.33 ± 2.51
9	A3	34.33 ± 2.08	38.66 ± 2.51
10	A4	37.67 ± 1.15	40 ± 2.64
11	A5	37 ± 2.65	36.66 ± 2.08
12	A6	39 ± 2	36 ± 1

Mouth dissolving study

Mouth dissolving test was performed for all the batches and all the batches were found to dissolved within 45 sec. batches with higher amount of polymers had comparatively high dissolving time as result reported in the Table no- 3.

Palatability study

All the batches were evaluated for the palatability study. The FDBFs were optimized on the basis of the taste, after bitterness and physical appearance. Because of Tadalafil is bitter in taste, taste masking the film was essential to improve patient acceptability. It was found that the addition of only (flavor and sweetener) pine apple as flavor and aspartame at various plasticizers did not mask the taste of the film. Formulations containing combinations of flavor, sweetener and taste masking agent M1, M4, A1 & A4 having +++ slightly bitter in taste, palatability study was reported in Table no-4.

Table4- Comparative evaluation of palatability study of FDBFs

Sr. No.	Formulation Code	Palatability Taste		
		Taste	After bitterness	Physical appearance
1	**M1**	+++	+++	Good
2	**M2**	++	+	Average
3	**M3**	++	+	Average
4	**M4**	+++	++	Good
5	**M5**	++	+	Average
6	**M6**	++	+	Average
7	**A1**	+++	++	Good
8	**A2**	+	+	Poor
9	**A3**	++	+	Poor
10	**A4**	+++	++	Good
11	**A5**	++	+	Poor
12	**A6**	++	+	Poor

In-vitro dissolution study

In-vitro dissolution study was carried out using USP XXIII apparatus type-2 (Elecrolab). The dissolution medium was 250 ml of phosphate buffer pH 6.8 the rotation speed was 50 rpm without the basket attached to it. The temperature of the dissolution media was maintained at 37º ± 05º C. During the study, 0.5 ml of aliquots was withdrawn at 4, 8, 12, 16 and 20, min and was replaced by fresh buffer. The aliquots were diluted at sufficient concentration with of phosphate buffer pH 6.8 and the amount of the drug release was analyzed spectrophotometrically at 284 nm. Results are shown in the Figure-4 and 5. Result showed all the batches release more than 90% of drug within 16 minutes. But the M1, M5 and A5 batches releases drug in the linear manner than the other batches. Higher amount of HPMC E-5 and E-15 resulted in release of drug at the slower rate. Figure no.4 shows the comparative dissolution profile of first 6 batches i.e. M1-M6 (Figure-4). Next batches i.e. A1 to A6 containing higher amount of HPMC E-15 shows slower drug release as compared to formulation containing lower amount of HPMC (Figure-5).

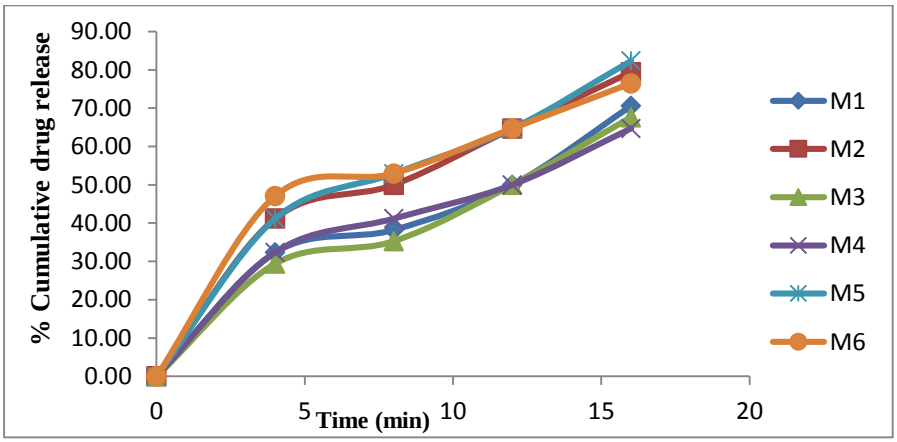

Figure 4-Comparative In-vitro Release Profile of Tadalafil Fast Dissolving Film

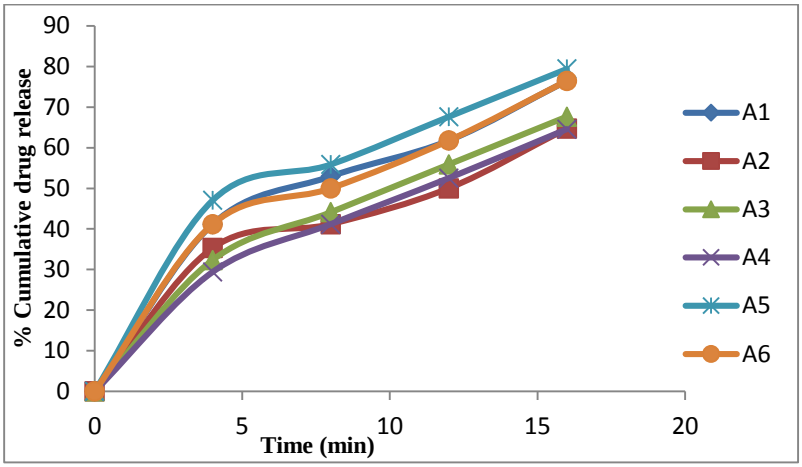

Figure 5-Comparative In-vitro Release Profile of Tadalafil Fast Dissolving Film

Stability studies

The stability study of the optimized batch M2, M5 and A5 was carried out at 65% relative humidity and 35 ^{0}C temperature for a period of 45 days. The batch was found be acceptable visually, mechanically with no change in in-vitro disintegration time of 36 s and minor change of mouth dissolving time of 48s.

The films did not show any significant changes in weight loss on storage and Tadalafil content. Also, in-vitro Tadalafil release profile of films of both the formulae (M2, M5 & A5) was not affected after storage.

Kinetic study

The (R^2) correlation coefficient values obtained for all four models are tabulated in Table-showing for zero order release, first order release Higuchi Matrix and Peppas release. The values for Higuchi matrix were closer to 1 than those for zero order, first order and Peppas. So, it was assumed that all the formulation followed Higuchi Matrix kinetics. The release was described the drug release, as a diffusion process based on the Flick's law, square root time dependent.

CONCLUSION

The fast dissolving buccal films of Tadalafil is rational in all the aspects of mouth dissolving dosage form. Pre-formulation studies of Tadalafil were performed; the FI-IR analysis revealed that excipients used compatible with Tadalafil. Effective film separation would be achieved using Petri-plate (wrapping with aluminum foil) as casting surface. The amount of plasticizer PEG-400 and propylene glycol was critical for film formation and separation properties. Tadalafil, a water insoluble and bitter drug could be successfully incorporated in the fast dissolving film, with the help of solubilizers such as tween-80 and taste masking was achieved in the optimized batch using combination of sweetener, flavor and taste masking agent. Optimized formulation passed all evaluation tests and scored better convenience than the marketed tablets of Tadalafil. It could be concluded that suitable packaging and storage conditions would be essential for Tadalafil containing FDBFs of Methanol.

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