IJMPR 2024, 8(11), 28-38

International Journal of Modern Pharmaceutical Research

www.ijmpronline.com

ISSN: 2319-5878
IJMPR
Research Article

SJIF Impact Factor: 6.669

FORMULATION AND EVALUATION OF CLOPIDOGREL BISULPHATE SUBLINGUAL FILM FOR THE TREATMENT OF ATHEROSCLEROSIS

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Article Received on: 20/09/2024

Article Revised on: 10/10/2024

Article Accepted on: 30/10/2024

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ABSTRACT

The present work involves the formulation of sublingual films of Clopidogrel, a BCS Class II drug, faces a major problem due to its poor bioavailability in oral dosage form. To increase solubility and bioavailability, Solid dispersion were prepared which is in the ratio 1:1, 1:3 and 1:5. The solubility of prepared solid dispersion varied from **0.09mg/ml to 0.59mg/ml** (SD1 to SD6). As compared to PVA, the solid dispersion prepared with CMC showed greater solubility which is in the ratio of 1:5. The drug content of prepared formulations of clopidogrel bisulfate solid dispersion with CMC was observed 94.9% and for solid dispersions with PVA, it was found to be 85.2%. Films prepared with HPMC E15 different concentrations were found to be flexible, smooth, translucent, non-sticky and homogeneous than HPMC E5 and HPMC E50. Folding endurance, thickness and tensile strength indicates that the Fast-dissolving Sublingual Films were mechanically stable. The Surface pH of all formulations was in the range of 6-7 and it is close to the saliva pH, these films are suitable for sublingual route with no irritation to the mucosa. The *In-vitro* drug release studies shows that release from the Fast-Dissolving Sublingual Films gets successfully released for over 10 mins. Drug release mechanism indicates that formulations had higher linearity in First order kinetics. Based on the results obtained from the physicochemical parameters and *in-vitro* drug release F2 was found to be best formulation.

KEY WORDS: Sublingual films, Clopidogrel Bisulphate, Solid dispersion, HPMC E15 and CMC.

INTRODUCTION

Clopidogrel bisulfate is a thienopyridine class inhibitor of $P2Y_{12}$ ADP platelet receptor.[1] Clopidogrel is used to treat individuals with a history of heart attack, stroke or recent stroke. It is also prescribed for those suffering from chest pain due to heart problems, poor circulation in the legs (peripheral arterial disease), acute coronary syndrome (ACS), and established peripheral arterial disease. By inhibiting platelet aggregation, Clopidogrel decreases the risk of arterial blockage, which helps prevent future heart attacks and strokes. Its role in managing cardiovascular disorders is crucial for reducing the incidence of these serious conditions.[2] However, the underperformance of antihypertensive therapies in major intervention trials, particularly in their effectiveness at reducing the incidence of coronary heart disease, has highlighted the need for novel dosage forms of cardiovascular drugs. This has led to the exploration and formulation of advanced delivery systems aimed at improving therapeutic outcomes in cardiovascular care.

Thrombosis superimposed on arteriosclerosis is a major cause of mortality and morbidity in patients with this condition. The use of antiplatelet agents and anticoagulants in managing arteriosclerosis is well-supported by numerous large randomized trials. In cases of coronary intervention, which is considered a medical emergency, the rapid attainment of therapeutic drug concentrations in the bloodstream and a swift onset of action are critical. Therefore, a fast-dissolving sublingual film of Clopidogrel could represent an optimal delivery method. Identifying an alternative delivery system that ensures prompt delivery, effective systemic distribution, and improved patient compliance is of utmost importance.

Fast-dissolving sublingual oral films or patches are considered an ideal solid dosage form for administering Clopidogrel in the treatment of heart disease.[3] Sublingual drug administration is well-established in the field of cardiovascular medications, as well as for steroids, certain barbiturates, and enzymes. Sublingual absorption offers significant advantages, as it bypasses the gastrointestinal system and liver, providing direct nutritional benefits. This is particularly important for individuals with gastrointestinal difficulties, such as ulcers, hyperactive gut, or coeliac disease, as well as those with compromised digestion, the elderly, and invalids. The sublingual route ensures that nutritional

benefits are achieved independently of gastrointestinal influences.[4]

The use of the sublingual route with fast-dissolving films facilitates rapid drug absorption, resulting in an immediate onset of action.[5] Sublingual drug administration has several advantages, including Improved patient compliance due to the elimination of associated pain with injections; administration of drugs in unconscious or incapacitated patients; convenience of administration as compared to injections or oral medications[6], The oral or buccal mucosa being highly vascularized can absorb drugs directly and possess easy access to the systemic circulation without undergoing hepatic first pass metabolism etc.,[7] Several techniques have been explored for the manufacturing of mucoadhesive buccal films, including solvent casting, hot melt extrusion, inkjet printing, and 3D printing Solvent casting technique is favored for its ability to produce high-quality buccal films while maintaining affordability and ease of execution.[8]

MATERIALS AND METHOD

Clopidogrel bisulphate was obtained as gift sample from Ultra laboratories, Hassan. HPMC E 5
HPMC E15 HPMC E50, Propylene glycol, Citric acid, Cross povidone and Xylitol obtained from Loba chemie Pvt. ltd Maharashtra and SD Fine chemical, Mumbai.

Materials used in this study

Table 1: Material used with their source.

Sl. No	Material	Property
1	Clopidogrel bisulfate	Pure drug
2	HPMC E 5	Film former
3	HPMC E15	Film former
4	HPMC E50	Film former
5	Propylene glycol	Plasticizer
6	Citric acid	Saliva stimulating agent
7	Cross povidone	Disintegrating agent
8	Xylitol	Sweetening agent

Equipment

Following equipment were used in the present study

Table 2: Equipment used with their source.

Sl. No	Name of the Instrument	Source
1	Electronic weighing balance	Radwag AS 220, Wagi Elektroniczne, Poland
2	Magnetic stirrer	Analytical technologies
3	Dissolution tester (USP)	TDT 08L, Electro lab, Mumbai, India
4	UV Visible Spectrophotometer	UV-1800, Shimadzu corporation, Japan
5	FTIR	Bruker alpha, Germany
6	Tensile strength	Universal material testing machine
7	Hot air oven	Analytical technologies

Methods

Preformulation studies

Preformulation is a group of studies that focus on the physicochemical properties of a new drug candidate that could affect the drug performance and the development of a dosage form.

Physical Appearance of Drug

Clopidogrel bisulphate was observed for colour, odour and physical state

Melting Point

The melting point was determined by Capillary tube method using Thales tube instrument. It was determined by taking small amount of drug in a capillary tube closed at one end and was inserted into a melting point apparatus in which the temperature can be measured when heated and temperature can be measured when heated and temperature at which the drug melts was recorded as melting point of drug.[9]

Solubility studies of pure drug in different solvents and different media

Solubility test for the drug Clopidogrel bisulphate was performed by using various solvents. Clopidogrel bisulphate is dissolved separately in little quantity of water, methanol, ethanol solvents and Phosphate Buffer pH 6.8, 7.4 and 0.1N HCL as medias.

Drug- Excipients compatibility Study

Drug-Excipients interaction plays a vital role in achieving stability of drug in dosage form. Fourier Transform Infrared Spectroscopy (FT-IR) was used to study the physical and chemical interactions between drug and excipients. FT-IR spectra of Clopidogrel bisulfate, HPMC E15 and Cross povidone and their

mixture were recorded using FTIR Bruker alpha, Germany

Analytical method used in the determination of Clopidogrel bisulfate

Standard calibration curve of Clopidogrel bisulphate in pH 6.8 phosphate buffer solution

100 mg of Clopidogrel bisulphate was dissolved in 100 ml of pH 6.8 phosphate buffer to give a concentration in 1mg/ml (1000µg/ml) 1 ml was taken and diluted to 100 ml with pH 6.8 phosphate buffer to give a concentration of 0.01 mg/ml (10µg/ml). From this stock solution aliquots of 2ml, 4 ml, 6 ml, 8 ml, 10 ml, were pipette out in 10 ml volumetric flask and volume was made up to the mark with pH 6.8 phosphate buffer to produce concentration of 20, 40, 60, 80 and 100µg/ml respectively. The absorbance of each concentration was measured at respective (λ_{max}) i.e., 290 nm in UV Double Beam Spectrophotometer.[10]

Preparation of solid dispersions

Kneading method

In ratio of 1:1, 1:3 and 1:5 solid dispersion of Clopidogrel bisulfate with CMC and PVA were prepared. Clopidogrel bisulfate and selected carries were transferred into motor then mixture was triturated with water and methanol (1:1) to form paste. At 40 ± 2^0 C the mixture was dried hot air The dried mass was pulverized to fine powder, sieve through sieve no.80. The prepared solid dispersion formulation was stored in desiccator for further studies.[11, 12]

Table 3: Formulation of Clopidogrel Solid Dispersion product.

Formulation code	Drug: polymer ratio	Clopidogrel	CMC (mg)	PVA (mg)	Methanol+water ratio (1:1)
SD1	1:1	100	-	100	10
SD2	1:3	100	-	300	10
SD3	1:5	100	-	500	10
SD4	1:1	100	100	-	10
SD5	1:3	100	300	-	10
SD6	1:5	100	500	-	10

Characterization of Prepared Solid Dispersions[13, 14]

Determination of equilibrium solubility

In solubility study, in conical flask Phosphate buffer pH 6.8 and distilled water were taken and excess amount of SDs were added and kept for shaking in rotary shaker for 48h to achieve equilibrium. 1ml aliquots were withdrawn and filter. Filtrate was analysed at 290nm against blank in UV Double Beem Spectrophotometer.

Drug content

Solid dispersion equivalent to 100mg of Clopidogrel bisulfate were weighed accurately and dissolved in the 100ml of Phosphate buffer pH 6.8. The solution was filtered, diluted and drug content was analysed at 290 nm and observation was recorded.

Formulation of Sublingual film containing Clopidogrel bisulfate solid dispersion

By Solvent Casting method

Fast-dissolving sublingual films were prepared using the solvent casting method. Initially, HPMC E15, the film-forming polymer, was dissolved in 20 mL of distilled water and stirred until the solution was clear. This solution was allowed to stand for one hour to ensure that any air bubbles were completely removed. Concurrently, a second solution was prepared by dissolving the drug, PEG 400 (plasticizer), citric acid (saliva-stimulating agent), cross-povidone (disintegrating agent) and xylitol (taste-masking agent) in a required quantity of distilled water. The two solutions were then combined and stirred for 1.5 hours. The resulting mixture was poured into a 7 cm petri dish and dried in a hot air oven at 37°C overnight. A film measuring 3×3 cm^2 was subsequently cut from the petri dish. The prepared films were evaluated for weight uniformity, thickness, tensile strength, drug content and dissolution characteristics.[15]

Table 4: Composition of fast dissolving sublingual film of Clopidogrel.

Ingredients(mg)	F1	F2	F3	F4	F5	F6
Clopidogrel Bisulphate	75	75	75	75	75	75
HPMC E15	200	300	--	--	--	--
HPMC E5	--	--	200	300	--	--
HPMC E50	--	--	--	--	200	300
Peg 400(ml)	0.5	0.5	0.5	0.5	0.5	0.5
Xylitol	10	10	10	10	10	10
Citric acid	50	50	50	50	50	50
Cross Povidone	20	20	20	20	20	20
Water (ml)	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S

Evaluation of Sublingual film

Physical evaluation

Film forming Capacity

The ability of film formers to create the desired films is characterized by their film-forming capacity, which can be classified as poor, average, good, or excellent.[16]

Weight variation

At three different places 9 cm^2 (3 x 3 cm) was cut from film. Individual film weights were taken for weight variation.[17]

Thickness

By the utilization of Digital Vernier thickness of the patch was measured at different position of the film and average was taken and standard deviation was calculated.

Folding endurance

Sublingual film was cut and folded repeatedly at same place until it broke. Without breaking the number of times, the fast-dissolving film could get folded at the same place will gives the folding endurance value.[18]

Tensile strength

For evaluation of film tensile quality (TS) of every formulation were taken and compute elasticity with the assistance of equation:

$$\textbf{Tensile strength} = \frac{\text{load at failure} \times 100\ \text{Film}}{\text{Thickness} \times \text{Film Width}}$$

Surface pH

The surface pH of the films was measured to assess potential irritation due to changes in pH in vivo, as an acidic or basic pH could cause discomfort to the buccal mucosa. The film was placed in a Petri dish, moistened with 1 mL of distilled water, and allowed to sit for 2 hours. The pH was then recorded using a pH meter, and the average of three measurements for each formulation was calculated.[19]

Disintegration time

The disintegration time limit is of 30 s or less for orally disintegrating tablets, as described in CDER guideline and can be applied to fast dissolving oral film. No official guideline is available for oral fast dissolving films. Typical disintegration time for film is 5-30 sec.

***In-vitro* Drug Release**

The drug release rate of fast dissolving sublingual film of Clopidogrel bisulphate was performed by the utilization of USP Type-I apparatus. The dissolution test was conducted using 900 ml Phosphate Buffer Solution pH 6.8, at 37 .5^{0}C with 50 rpm of the Basket speed. Aliquot 5 ml of the solution was collected at time interval of 10 min for 1 hour and at the same time replace with 5 ml or same amount of fresh dissolution medium. Using Whatman filter paper aliquots were filtered and the absorbance measured at 290 nm.[20]

RESULT AND OBSERVATION

Preformulation studies

Table 5: Physical characterization of Clopidogrel bisulphate.

Sl. No	Parameter	Observations
1	Odour	Odourless
2	Colour	White
3	Appearance	Amorphous

Melting point

Table 6: Melting point determination of Clopidogrel Bisulphate.

Sl. No	Mean ± SD (n=3)
1	183±2.5

Drug-Excipient compatibility study

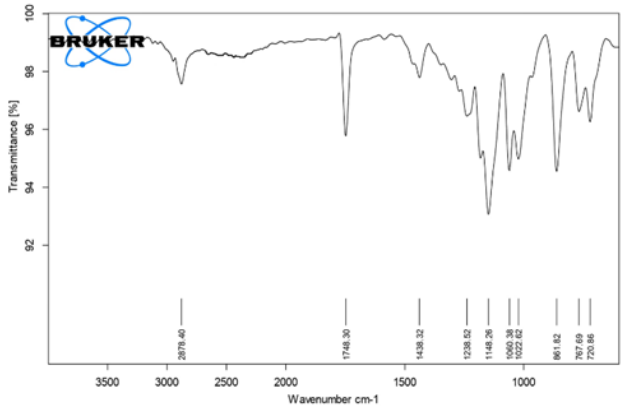

Figure 1: IR of Pure Clopidogrel Bisulfat

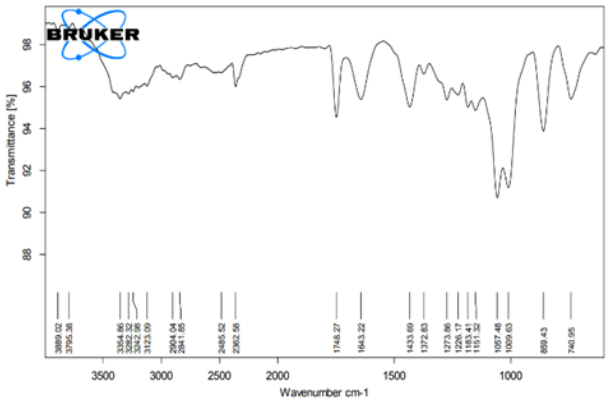

Figure 2: IR of Clopidogrel + Crospovidone

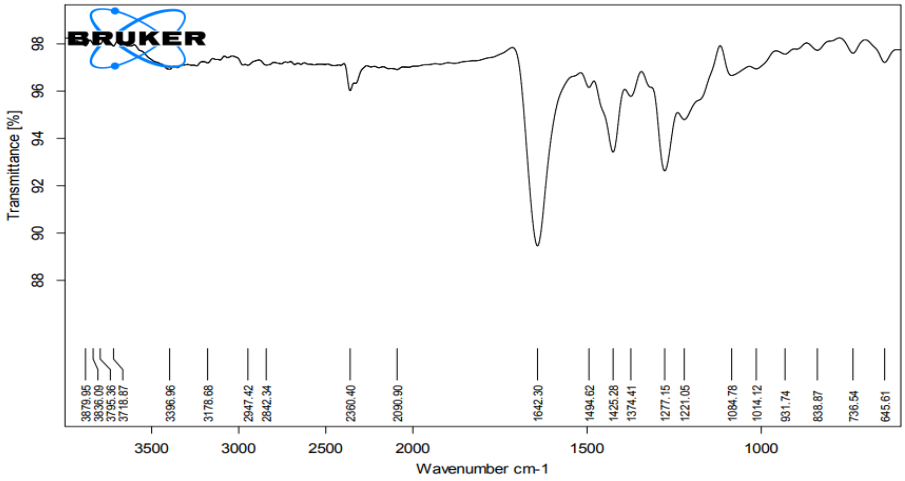

Figure 3: IR of Physical mixture.

Solubility studies

Table 7: Solubility study of Clopidogrel bisulphate in different media. (n=3)

Drug	Solubility in distilled water mg/ml	Solubility in 0.1N HCL mg/ml	Solubility in phosphate buffer (pH 6.8) mg/ml	Solubility in phosphate buffer (pH 7.4) mg/ml
Clopidogrel	0.02±0.87	75.17±0.64	0.19±0.72	0.09±0.45

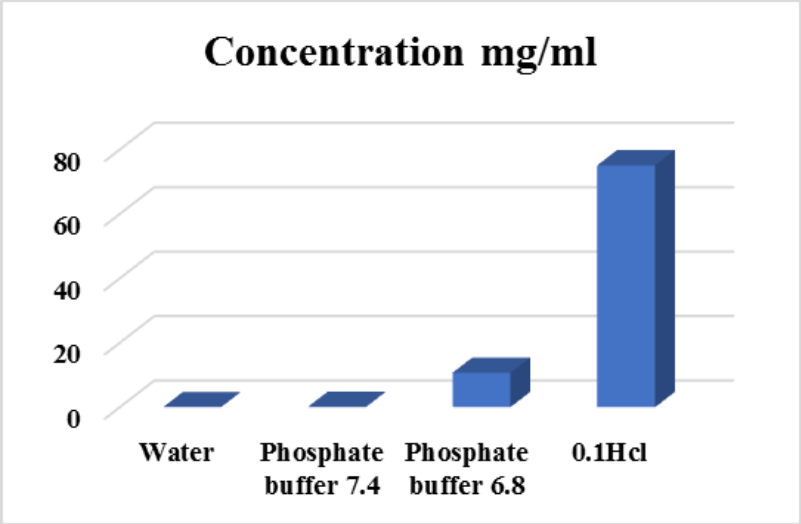

Figure 1: Solubility study of Clopidogrel in different media.

Determination of Equilibrium Solubility and % Drug content of SDs.

Table 8: Saturation Solubility Study and Drug Content of Various Formulations.

Sl. No	Formulation code	Saturation solubility in water (mg/ml)	Folds increased	% Drug content
1	Pure drug	0.02	-	-
2	SD1	0.09±0.87	4.5	76±0.12
3	SD2	0.12±0.14	6	79±0.25
4	SD3	0.25±0.76	12.5	85±0.19
5	SD4	0.18±0.106	9	81±0.16
6	SD5	0.32±0.53	16	89±0.35
7	SD6	0.59±0.49	25	94.9±0.41

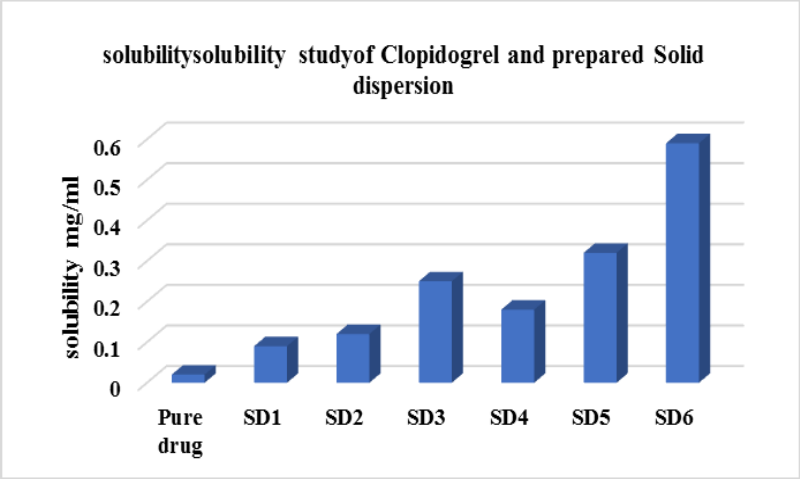

Figure 2: Comparison of solubility study profile of Clopidogrel and prepared Solid dispersion.

Calibration curve of Clopidogrel in Phosphate buffer pH 6.8

Table 9: Standard Calibration curve of Clopidogrel bisulfate.

Concentration	Absorbance
0	0
2	0.163
4	0.323
6	0.489
8	0.660
10	0.828

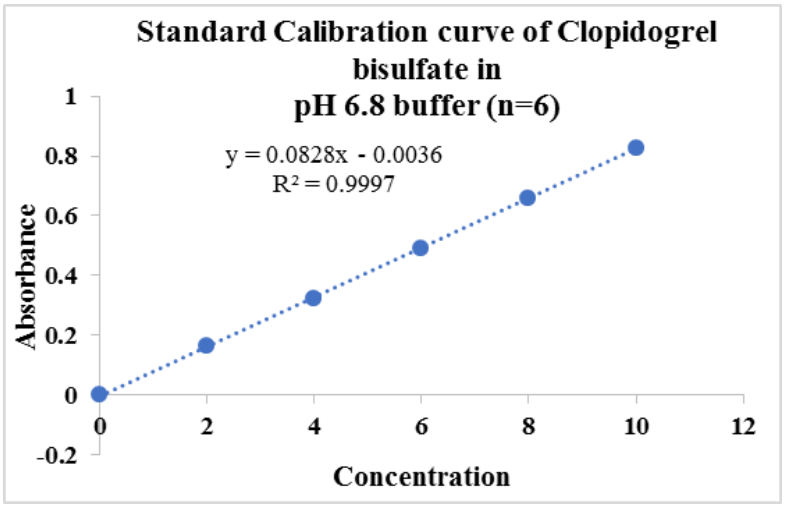

Figure 3: Calibration curve of Clopidogrel in Phosphate buffer pH 6.8.

Evaluation of fast dissolving Sublingual film

Physicochemical evaluation

Table 10: Film forming capacity of different formulations.

Sl. No	Formulation code	Film forming capacity
1	F1	Excellent
2	F2	Excellent
3	F3	Good
4	F4	Good
5	F5	Average good
6	F6	Average good

Table 11: Other evaluation of Fast Dissolving Sublingual films(n=3).

Formulation code	Thickness (mm) ±RSD (%)	Folding endurance (%) ±RSD (%)	Tensile strength (N/mm^2) ±RSD (%)	Weight Uniformity (mg) ±RSD (%)	Surface pH ±RSD (%)
F1	0.136±0.029	121.0.15	1.05	95±0.13	6.7±0.74
F2	0.130±0.028	136±0.81	1.24	99.2±0.08	6.8±0.97
F3	0.134±0.027	130±0.81	1.35	90.23±0.13	6.5±0.42
F4	0.131±0.031	124±0.35	1.14	96.5±0.12	6.8±0.12
F5	0.147±0.027	139±0.95	1.32	93.46±0.10	6.6±0.97
F6	0.138±0.024	143±0.5	1.48	94.16±0.11	6.5±0.74

Figure 4: Tensile Strength Evaluation.

Table 12: *In-vitro* disintegration time and drug content.

Formulation code	Disintegration time(sec)	Drug content (%)
F1	41±1.24	88.817±0.47
F2	28±1.34	93.75±0.23
F3	15±2.49	92.9±0.19
F4	61±1.15	93.75±0.83
F5	19±3.3	90.97±0.16
F6	30±1.63	92.72±0.26

***In-Vitro* Dissolution Studies**

Table 13: *In-vitro* dissolution studies of Fast Dissolving Sublingual Films from F1 to F6 in Phosphate buffer 6.8.

Time (mins)	% Drug Release					
	F1	**F2**	**F3**	**F4**	**F5**	**F6**
0	0	0	0	0	0	0
2	29.11±0.65	31.18±0.76	25.60±0.95	26.58±0.73	22.89±0.71	23.70±0.65
4	43.62±0.32	48.52±0.92	40.43±0.61	43.25±0.22	38.43±0.34	39.43±0.79
6	67.20±0.78	70.13±0.48	61.37±0.73	64.47±0.71	55.74±0.31	58.11±0.43
8	81.77±0.56	84.89±0.21	79.08±0.95	80.75±0.42	73.96±0.99	75.34±0.66
10	95.05±0.25	97.55±0.45	92.97±0.78	93.47±0.84	89.65±0.78	90.26±0.52

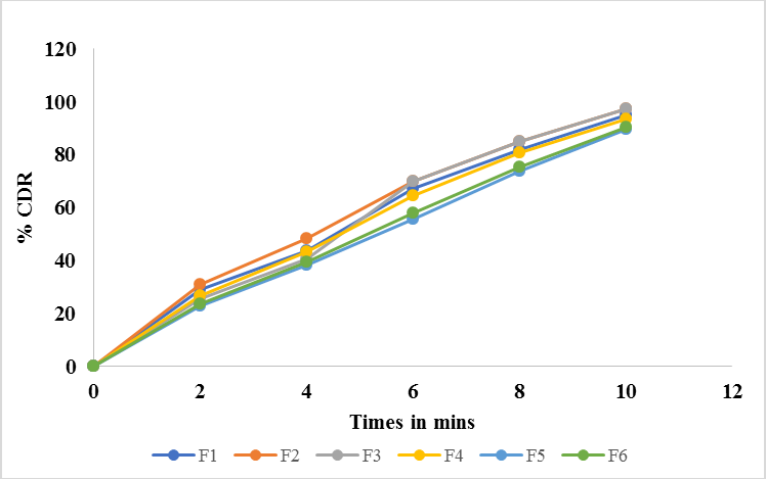

Figure 4: *In-vitro* dissolution studies of Fast Dissolving Sublingual Films from F1 to F6 in Phosphate buffer 6.8

Different drug kinetics Models

Table 14: First order kinetics for *in-vitro* drug release of formulation F1 to F6.

Time (min)	Log % Drug Remaining					
	F1	F2	F3	F4	F5	F6
0	2	2	2	2	2	2
2	1.851	1.838	1.872	1.866	1.887	1.883
4	1.751	1.712	1.775	1.754	1.789	1.782
6	1.516	1.475	1.587	1.551	1.646	1.622
8	1.261	1.179	1.381	1.284	1.416	1.392
10	0.695	0.389	0.847	0.797	1.015	0.989

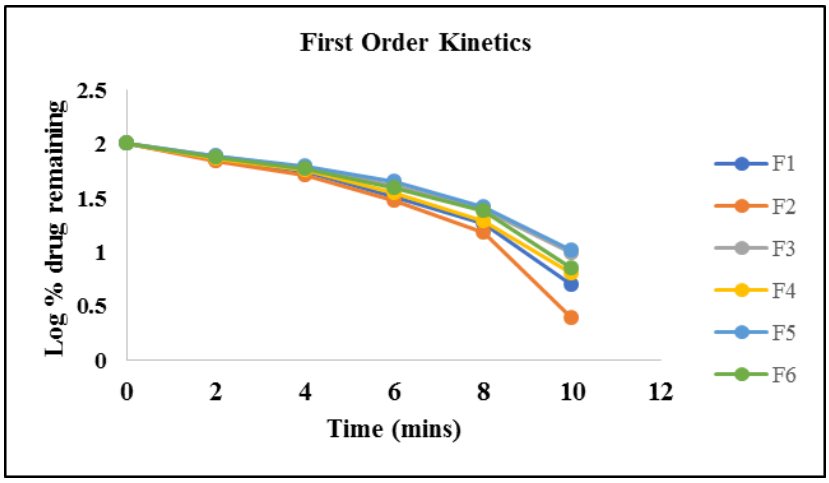

Figure 5: First order kinetics for *in-vitro* drug release of formulation F1 to F6.

Table 15: Higuchi model for *in-vitro* drug release of formulation F1 to F6.

√t (min)	% Drug Release					
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
1.414	29.11	31.18	25.6	26.58	22.89	23.7
2.000	43.62	48.52	40.43	43.25	38.43	39.43
2.449	67.2	70.13	61.37	64.47	55.74	58.11
2.828	81.77	84.89	79.08	80.75	73.96	75.34
3.162	95.05	97.55	92.97	93.47	89.65	90.26

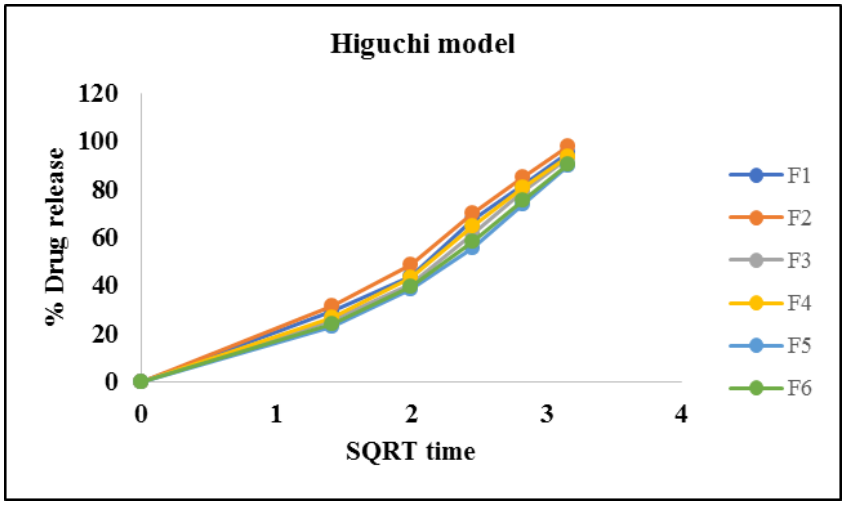

Figure 6: Higuchi model for *in-vitro* drug release of formulation F1 to F6.

Table 16: Peppas model for *in-vitro* drug release of formulation F1 to F6.

Log Time	% Log release					
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
0.301	1.464	1.494	1.408	1.425	1.360	1.375
0.602	1.6997	1.6859	1.6067	1.6360	1.5847	1.5958
0.778	1.8274	1.8459	1.7880	1.8094	1.7462	1.7643
0.903	1.9126	1.9289	1.8981	1.9071	1.8690	1.8770
1.000	1.9780	1.9892	1.9683	1.9707	1.9526	1.9555

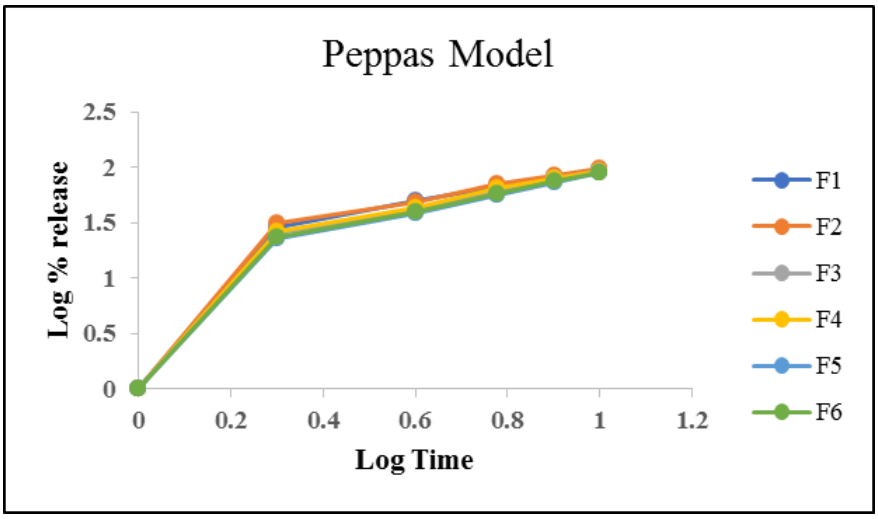

Figure 7: Peppas model for *in-vitro* drug release of formulation F1 to F6.

Table 17: Regression co-efficient (R^2) values and 'n' values of formulation according to different kinetic models.

Formulation Code	Zero Order		First Order		Higuchi	Peppas	
	R^2	n	R^2	n	R^2	R^2	n
F1	0.9808	9.270	0.8760	0.338	0.9735	0.9962	0.7726
F2	0.9781	9.578	0.8760	0.336	0.9731	0.9960	0.7724
F3	0.9849	9.931	0.8708	0.343	0.9377	0.9823	0.8709
F4	0.9885	9.301	0.9276	0.259	0.9573	0.9962	0.8001
F5	0.9971	8.839	0.9198	0.213	0.9367	0.9967	0.8552
F6	0.9956	8.927	0.9265	0.220	0.9437	0.9971	0.8417

DISCUSSION

In this present study fast dissolving sublingual film of Clopidogrel bisulphate was prepared by enhancing solubility by Solid dispersion method. Films were formulated by using HPMC E5, HPMC E15 and HPMC E50 in different ratios by utilizing Solvent casting technique. Later the formulations were evaluated for different physicochemical parameters.

Result of physical characterization of Clopidogrel bisulphate is listed in **Table 5.** No variation was found in its specification and observation recorded at the time of experimentation. The melting point of Clopidogrel bisulphate complies with reported melting point in literature i.e. 183±2.5**(Table 6)**.

Solubility studies of pure Clopidogrel in distilled water, 0.1N HCL, phosphate buffer pH 6.8 and 7.4 shown in **Figure 1**. The solubility of drug in water (0.02±0.87), 0.1N HCL (75.17±0.64), phosphate buffer pH 7.4 (0.19±0.72) and 6.8 (0.09±0.45). As per this result Clopidogrel shows very less solubility in water compared to other medias **Table 7.** The data of solubility study of prepared solid dispersion (SD1 to SD2) is represented **Table8** and shown in **Figure 2**. By solid dispersion technique the solubility of drug was enhanced. The solubility of prepared solid dispersion varied from **0.09mg/ml to 0.59mg/ml** (SD1 to SD6). As compared to PVA, the solid dispersion prepared with CMC showed greater solubility which is in the ratio of 1:5. The drug content of prepared formulations of clopidogrel bisulfate solid dispersion with CMC was observed 94.9% and for solid dispersions with PVA, it was found to be 85.2% **(Table 8)**.

The calibration curve of Clopidogrel was developed in the range of 2-10µg/ml at wavelength of 290nm. The standard calibration curve obeys Beer-Lambert's law, gives linear curve and the R^2 value is not greater than 0.999. The results are shown in **Table 9** and **Figure 3**.

The drug excipient compatibility was studied by FT-IR Spectroscopy (BRUKER ALPHA E) shown in **Figure 1-3**. The IR spectra of physical mixture show sharp peak at 1014 cm-1 is due to presence of -CO stretching. 3178 cm-1 is due to presence of N-H stretching. 3836 cm-1 is due to presence of -OH stretching. 1642 cm-1 is due to presence of C=C stretching. 2090 cm-1 due to presence of C=O stretching, there is no deviation in the peak position. Hence it shows drug and excipients are compatible with each other.

Films prepared with HPMC E15 different concentrations were found to be flexible, smooth, translucent, non-sticky and homogeneous than HPMC E5 and HPMC E50. The drug and polymer distribution were uniform. **(Table 10).** Folding endurance, thickness and tensile strength indicates that the Fast-dissolving Sublingual Films were mechanically stable. The Surface pH of all formulations was in the range of 6-7 and it is close to the saliva pH, these films are suitable for sublingual route with no irritation to the mucosa **(Table 11).**

The *In-vitro* drug release studies shows that release from the Fast-Dissolving Sublingual Films gets successfully released for over 10 mins. Drug release mechanism indicates that formulations had higher linearity in First order kinetics. By fitting in the Korsmeyer- Peppas equation the release kinetics follows non Fickian kinetics **(Table 13-17)**. Based on the results obtained from the physicochemical parameters and *in-vitro* drug release F2 was found to be best formulation.

CONCLUSION

By considering the results of the present work revealed that, Solid dispersion technique can be used successfully to improve the dissolution and bioavailability of poorly water-soluble drug Clopidogrel and SD6 formulation was incorporated into the fast-dissolving Sublingual films. By observing the results of *In-vitro* drug release, it can be suggested for *In-vivo* and *Ex-vivo* study for future scope. For providing patients with most convenient mode of administration, we have made an attempt to formulate Fast Dissolving Sublingual Films of Clopidogrel, which is not available in the market and films were dissolve in saliva without need of water which shows rapid onset of action.

ACKNOWLEDGEMENT

Author is thanking full to SJM College of Pharmacy, Chitradurga for their support and encouragement. And also for BIET Davanagere for permitting utilization of equipment for the study. I express my gratitude to Ultra laboratories, Hassan for providing drug sample.

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