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FORMULATION AND EVALUATION OF ORAL FAST DISSOLVING FILM OF AN ANTI-DIABETIC DRUG GLIPIZIDE

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ABSTRACT

The present study was to formulated and evaluated oral fast dissolving film of glipizide for the treatment of diabetes mellitus. Glipizide comes as tablets and extended-release(long acting) tablets to take by mouth.Glipizide is used along with diet and exercise,some times with other medication, to treat type 2 diabetes (condition in which body does not use insulin normally and, therefore, can not control the amount of sugar in the blood). Glipizide is in a class of medications called sulfonylureas. Film are thin and semisolid in nature. The film form can be swallowed easily with the connected of saliva fluid and they are disintegrate rapidly and quick absorbed by buccal mucosa. Medicated film of glipizide was formulated using polymer like, HPMC, carbocol. The prepared medicated film were evaluated for their physic- chemical properties like surface pH, thickness, folding endurance, drug release and drug content. G2 formulation was the best obtained formulation.

KEYWORDS: Glipizide, Material and methods, Discussion, Conclusion.

INTRODUCTION

The geriatric and pediatric patients who experienced difficulties in swallowing traditional oral solid-dosage forms are now treated with the fast dissolving drug-delivery systems which was developed in the late 1970s as an alternative to capsules, tablets and syrups. As there are many benefits of the film such as fast, accurate dosing, safe efficacy, convenience, portability, etc. So the fast dissolving oral films are used as practical mutually exclusive to orally transmitted over the counter medicines. Rapid absorption of the drug is potential as the fast dissolving oral film utilise sublingual route, which lastly lead to immediate onset of drug action.[1]

Fast dissolving oral films are the most advanced form of oral solid doses form. Mouth dissolving film formed of a very lean oral strip, that is just located on the patient tongue an oral mucosal tissue and moist by saliva. Fast dissolving films are accurate safe dosing in efficacious format convenient and portable, without need for water. Oral thin films are disintegrate an patient's tongue in a few seconds for rapid release of one or more pharmaceutical active ingredients.[2,3,4]

MATERIAL AND METHODS

Drug: Glipizide provide by SUPRA CHEMICAL jubilant generics limited.

1. Chemical list: Table No-1: List of Chemical Used.

S.no.	ITEM	MANUFACTURERS
1. Drug		
I	Glipizide	Supra Chemicals, Navi Mumbai
2. Polymers		
Ii	HPMC E15	Yarrow Chem Products
Iii	HPMCK100	Yarrow Chem Products
Iv	HPMCK4M	Yarrow Chem Products
V	B-Cyclodextrin	
3. Equipments		
Vi	Screw gauge	
Vii	Ultrasonic bath Sonicator	PCi, Mumbai
Viii	Stirrer	REMI
iX	UV-spectrophotometer	SHIMADZU 1700
Xi	Digital weight balance	VIBRA, Shinko Denshi CO.LTD
Xii	Vernier caliper	Asian Contec Ltd

Xiii	Dissolution test apparatus	VEEGO

METHODOLOGY

Solid dispersion

solid dispersion is prepared by following kneading technique, the Glipizide with beta-cyclodextrin weighted in the ratio of 1:4. The weighted amount of Glipizide and beta cyclodextrin were moistened with methanol to get homogenous slurry, using vaccum evaporation methanol was removed. The obtained mass transferred to the vaccum desicator and dried to constant weight. The dried product was pulverized and it sifted through sieve# 100. Product samples prior to be used for the study and stored in the desicator.

Prepration of fast dissolving film

Accurately weighed quantities of film forming polymers such as HPMC of various grades, plasticizers, sweetener, salivary stimulating agent and flavoring agent were dissolved in distilled water and resulting dispersion was stirred for 90 min at 70°C. The resulting product was kept for drying for 24 hrs. The dispersion was casted onto the glass mould and allowed to dry under vacuum. The mould in size of 5×5 cm2 and the mould capacity of 16 mL was used to obtain a thin flexible rapid dissolving film. In initial attempts placebo films were prepared by omitting GLIPIZIDE. Later, the optimized GLIPIZIDE: β-Cyclodextrin solid dispersion (1:4 ratio) with equivalent weight 25 mg of glipizide was added to the formulation (Table 1) to obtain FDF of GLIPIZIDE. After sufficient drying, film was cut into 2×2 cm2square strips. The prepared square thin film strips were stored in a desiccator for further studies.

Table 2: Composition of fast release oral film.

Formulation	G1	G2	G3	G4	G5	G6
Drug:β-cyclodextrine(mg)(1:4 ratio)	25	25	25	25	25	25
HPMC K4m	100	120	-	-	-	-
HPMC K15m	-	-	100	120	-	-
HPMC K100	-	-	-	-	100	120
PEG	40	30	40	30	40	30
Aspartame	10	5	10	5	10	5
Citric acide	10	5	10	5	10	5
Cross povidone	5	5	5	5	5	5
Water uo to quntity sufficient	qs	qs	qs	qs	qs	qs

RESULT

1. Physical Appearance

Table 1.1: Physical Parameter of Glipizide.

S.No	Parameter	Observation
1	Color	White
2	Odour	Odourless
3	Taste	Tastless
4	Texture	Crystalline

2. Melting Point

Table 2.1: Melting Point of Glipizide.

S.No.	Average (ºC)	Melting Point ±S.D
1.	200-201	201± 1.12
2.	201-202	
3.	201-202	

3: Solubility Studies

Table 3.1: Solubility studies of drug in different solvent.

S. No.	Solvents	Solubility
1	Chloroform	Soluble
2	Methanol	Sparingly Soluble
3	Distilled water	Insoluble
4	Ethanol	Insoluble
5	IPA	Slightly soluble
6	Acetone	Slightly soluble
7.	DCM	Slightly soluble

Table 3.2: Saturation state solubility study.

Solvent media	Solubility in µg/ml
Solubility in distilled water	3.70
Solubility in 0.1 N HCl	10.11
Solubility in phosphate buffer pH 6.5	6.75
Solubility in phosphate buffer pH 7.4	4.23

Excess amount of drug was dissolved in 10 ml of water and it was shaken properly and it was kept for 48 – 72 hours for complete hydration. After 72 hours the solution was again shaken properly and filtered. The filtrate was analyzed by UV double beam Spectrophotometer by taking absorbance at wavelength 276 nm.

4. PARTITION COEFFICIENT

In phosphate buffer pH-7.4

- 25ml n- Octanol and 25ml of phosphate buffer pH-7.4 and 25mg drug were taken in a separating funnel and shaken well for about 30 minute. Then allowed to separate both layer and aqueous layer, the absorbance was taken at 274.5 nm.
- Absorbance was found to be = 0.169
- Partition coefficient (log P) value found to be =1.229

In phosphate buffer pH-6.5

- 25ml n- Octanol and 25ml of phosphate buffer pH-6.5 and 25mg drug were taken in a separating funnel and shaken well for about 30 minute. Then allowed to separate both layer and aqueous layer, the absorbance was taken at 274.5 nm.
- Absorbance was found to be = 0.622
- Partition coefficient (log P) value found to be =1.29

In pH-0.1 N HCl buffer

- 25ml n- Octanol and 25ml of pH-0.1 N HCl buffer and 25mg drug were taken in a separating funnel and shaken well for about 30 minute. Then allowed to separate both layer and aqueous layer, the absorbance was taken at 274.5 nm.
- Absorbance was found to be = 0.115
- Partition coefficient (log P) value found to be=1.37

5. QUANTITATIVE ESTIMATION OF DRUG

Table 5.1: Preparation of Calibration Curve Of Glipizide In Distilled Water at λ_{max} 274.5 nm

S.NO.	Concentration (µg/ml)	Absorbance (λ_{max} 274.5 nm)
1	2	0.029
2	4	0.035
3	6	0.046
4	8	0.068
5	10	0.087

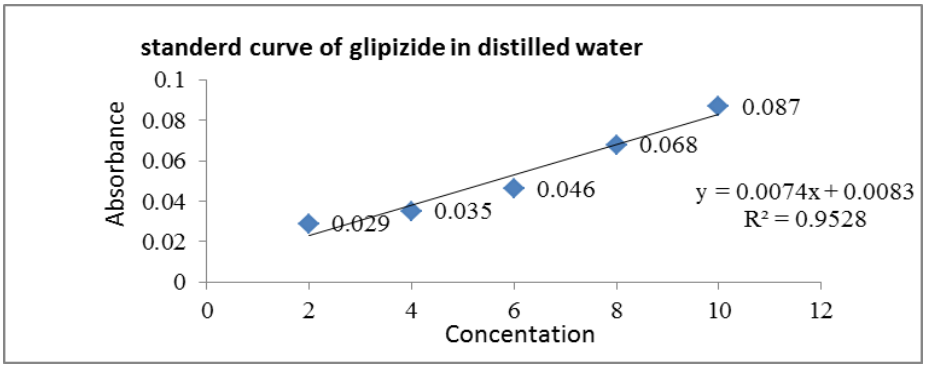

Fig. 5.1: calibration curve of Glipizide in distilled water.

Table5.2: Preparation of Calibration Curve of Glipizide In phosphate buffer Ph 6.5 at λ_{max} 274.5 nm.

S.No.	Concentration (µg/ml)	Absorbance (λ_{max} 274.5 nm)
1	2	0.031
2	4	0.039
3	6	0.066
4	8	0.088
5	10	0.105

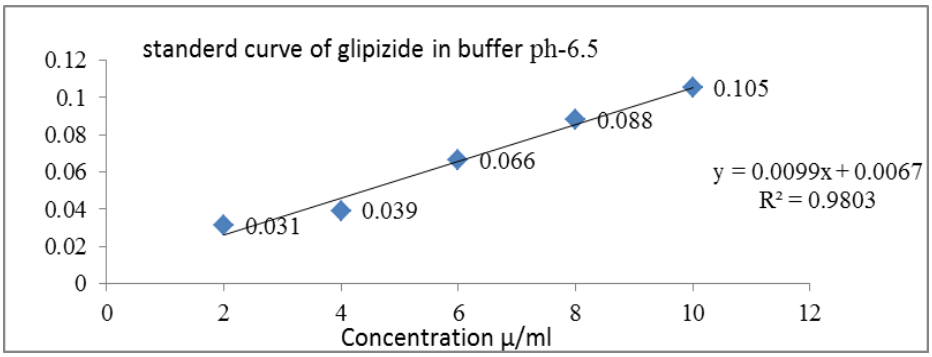

Fig. 5.2: Calibration curve of Glipizide in phosphate buffer ph-6.5 at λ_{max} 274.5 nm.

Table 5.3: Preparation of Calibration Curve of Glipizide.

S.No.	Concentration (µg/ml)	Absorbance (λ_{max} 274.5 nm)
1	2	0.021
2	4	0.026
3	6	0.032
4	8	0.046
5	10	0.048

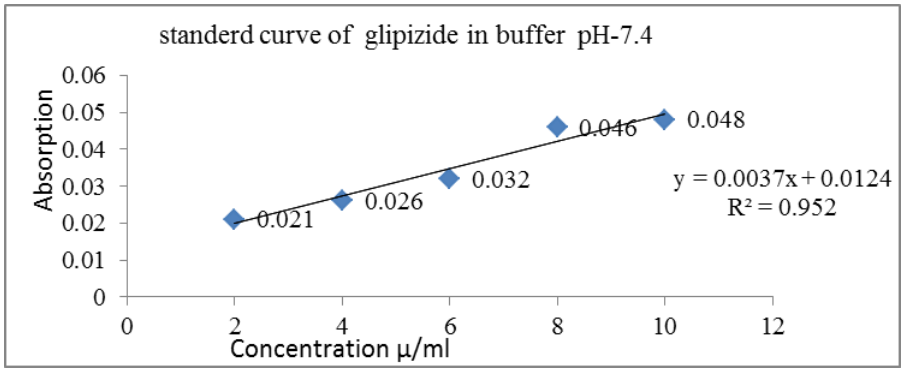

Fig. 5.3: Calibration Curve of Glipizide In Phosphate Buffer pH-7.4 at λ_{max} 274.5 nm.

Table 5.4: Calibration Curve Of Glipizide In 0.1 N Hcl Buffer at λ_{max} 274.5 nm.

S.NO.	Concentration (µg/ml)	Absorbance (λ_{max} 274.5 nm)
1	2	0.004
2	4	0.008
3	6	0.016
4	8	0.021
5	10	0.031

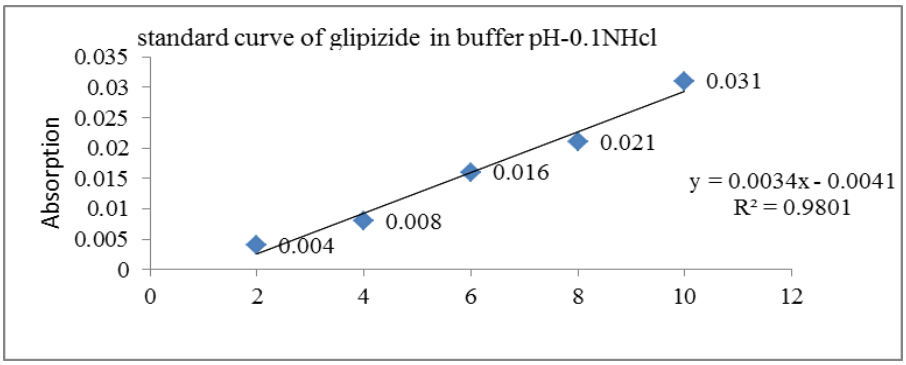

Fig. 5.4: Calibration Curve Of Glipizide In Phosphate Buffer Ph-0.1N Hcl at λ_{max} 274.5nm.

Partition coefficient

Table no5.5: Effect of PH on partition coefficient of glipizide.

S.No.	Buffer pH	Partition coffecient
1	7.4	1.229
2	6.5	1.29
3	0.1N Hcl	1.37

6. Drug excipients compatibility study through FTIR

Drug excipients/ polymers and their physical mixture was evaluated by the FTIR spectra analysis after completion of 21 days as per protocol.

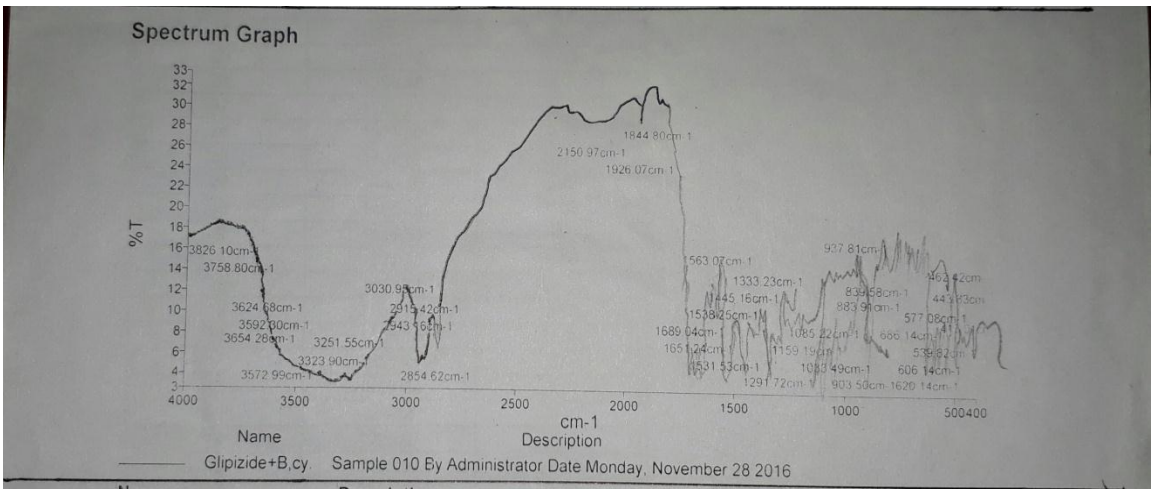

Fig. 6.1: FTIR Spectra of drug+β-cyclodextrine.

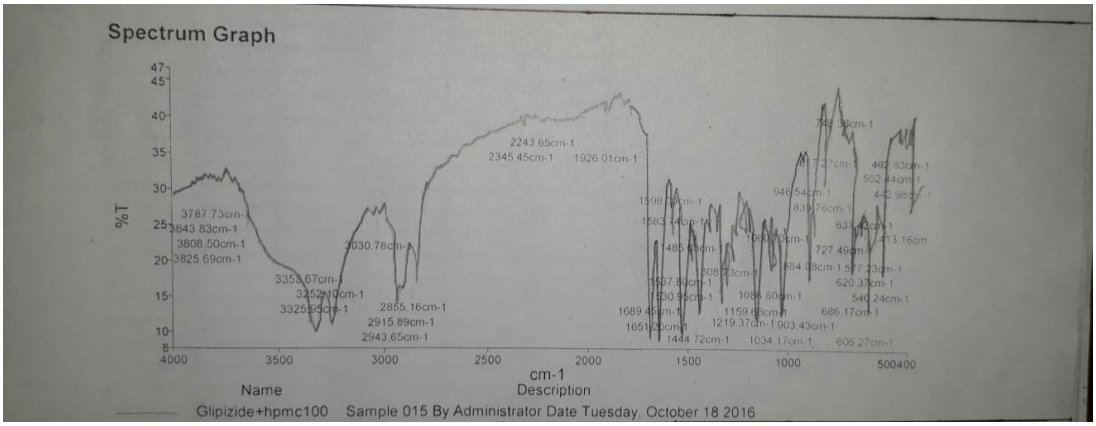

Fig. 6.2: FTIR spectra of drug+hpmc100.

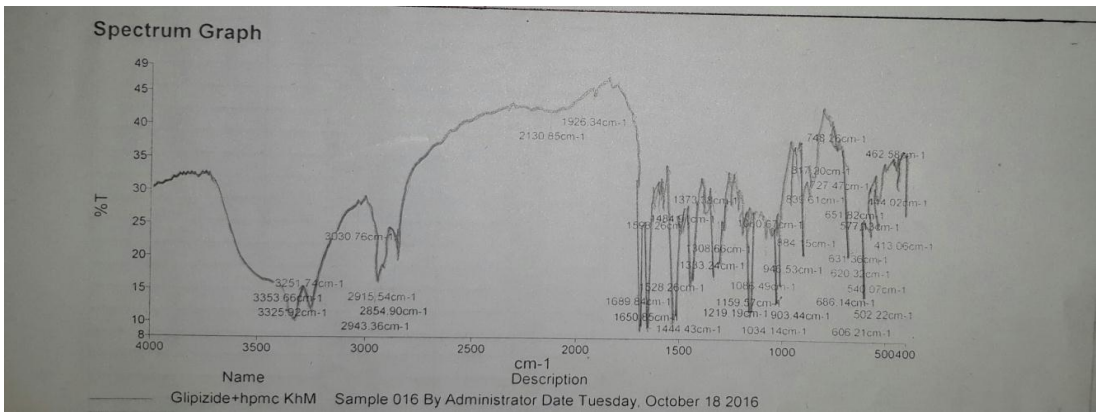

Fig. 6.3: FTIR Spectra of drug+hpmck4m.

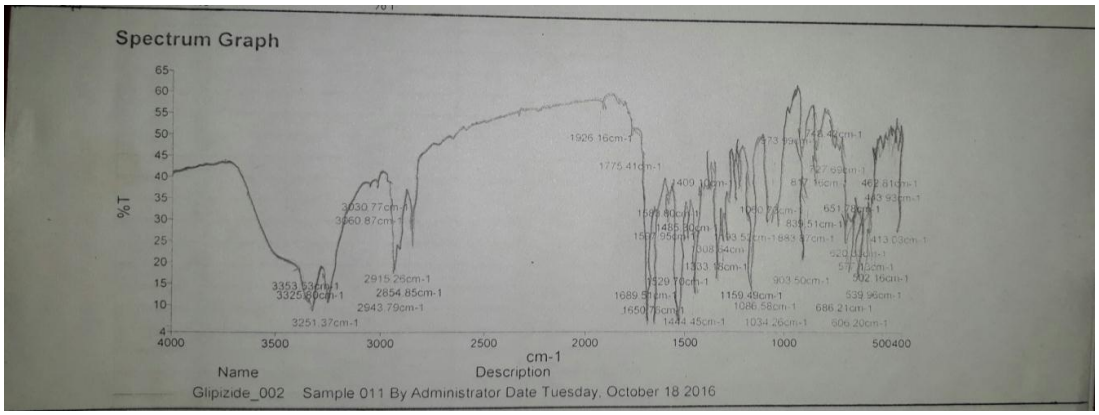

Fig. 6.4: FTIR spectra of Glipizide.

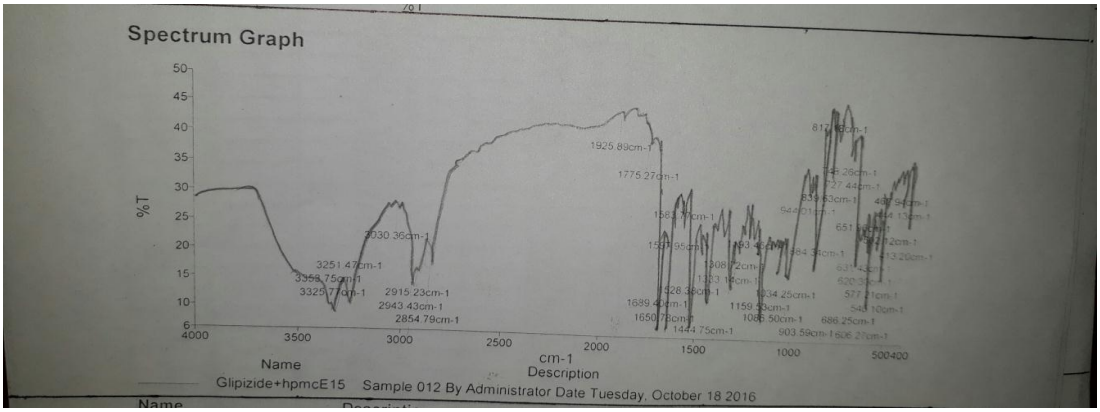

Fig. 6.5: FTIR spectra of drug+hpmc E15.

7. SEM Analysis of Glipizide fast dissolving film

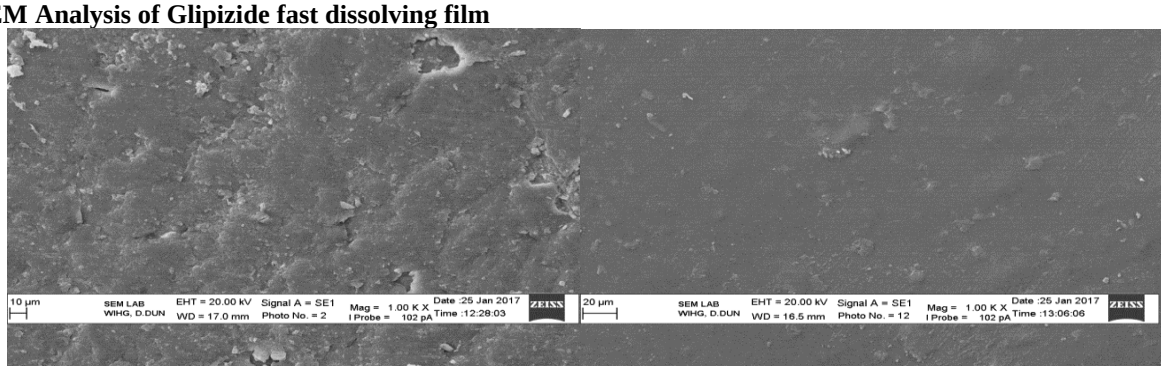

Fig. 7.1: SEM analysis of G1 formulation.

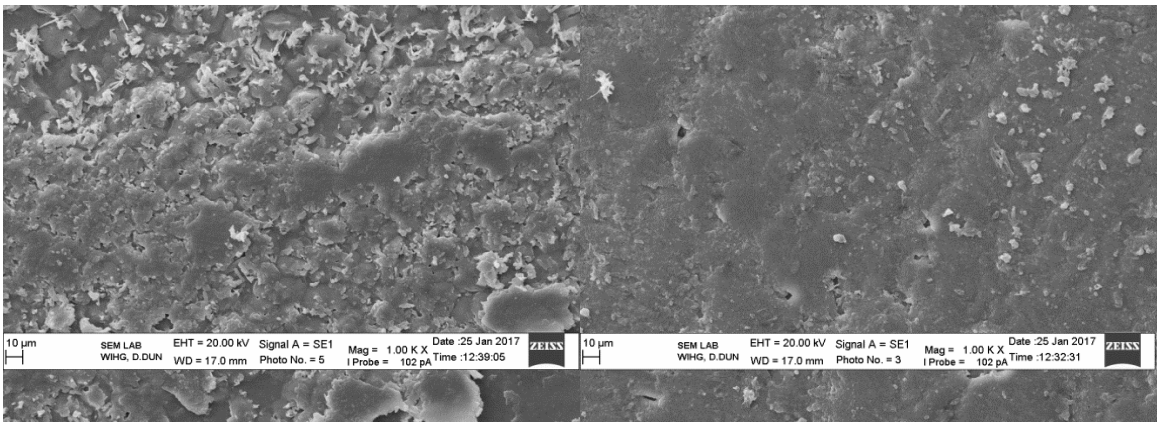

Fig. 7.2: SEM analysis of G2 formulation.

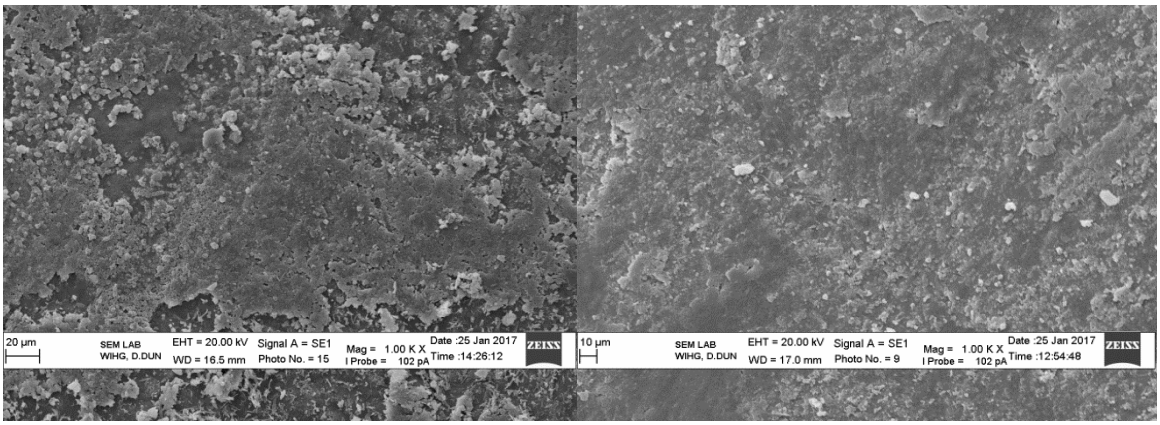

Fig. 7.3: SEM analysis of G3 formulation.

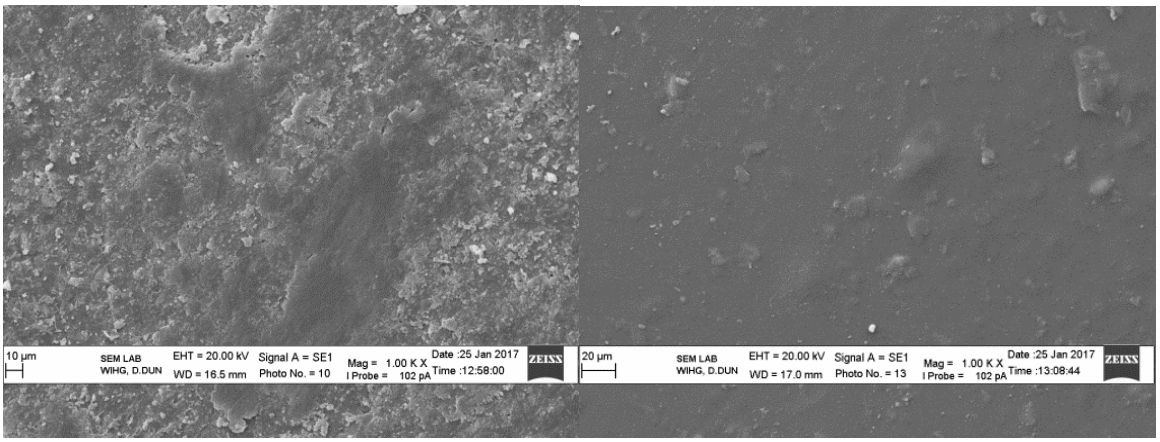

Fig. 7.4: SEM analysis of G4 formulation.

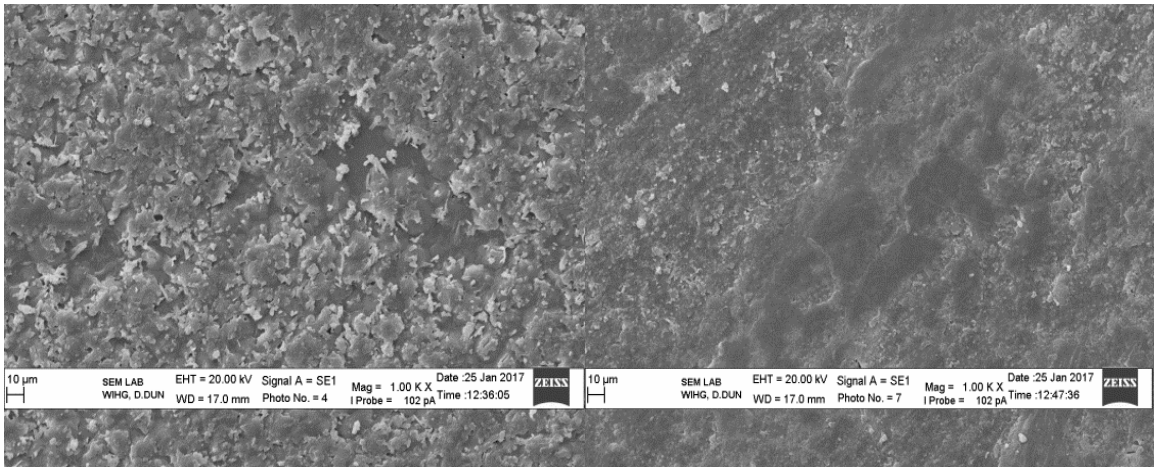

Fig7.5: SEM analysis of G5 formulation.

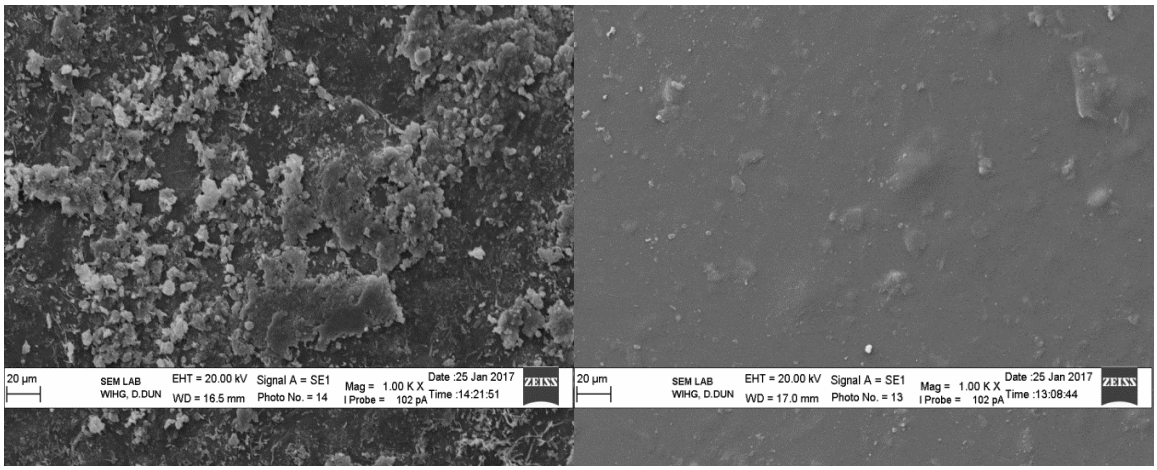

Fig. 7.6: SEM analysis of G6 formulation.

8. Evaluation study

Table no.8.1 : Evaluation parameters of the prepared buccal patch.

Formulation	Weight uniformity ± SD	Folding endurance± SD	Thickness ± SD	Disintegration time (in second) ±SD
G1	0.181±0.0015	183±3.21	3.069±0.0087	49±5.56
G2	0.186±0.0015	188±2.51	3.086±0.0096	35±0.57
G3	0.183±0.0021	189±1.73	3.067±0.0094	36±2.30
G4	0.183±0.0021	181±3.5	3.067±0.0014	55±3.0
G5	0.182±0.0024	182±1.41	3.074±0.0010	52±2.51
G6	0.182±0.0027	176±1.52	3.071±0.0013	46±1.52

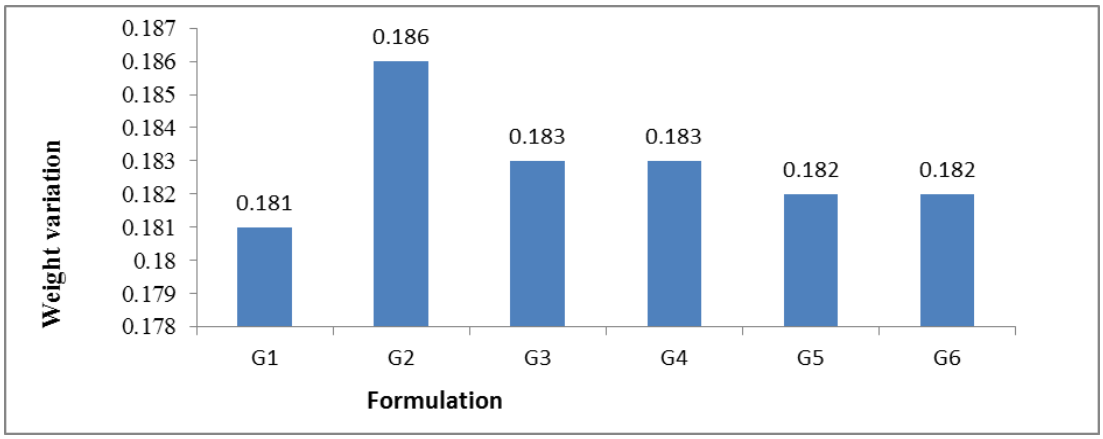

Fig. 8.1: Weight variation of prepared formulation of fast dissolving film.

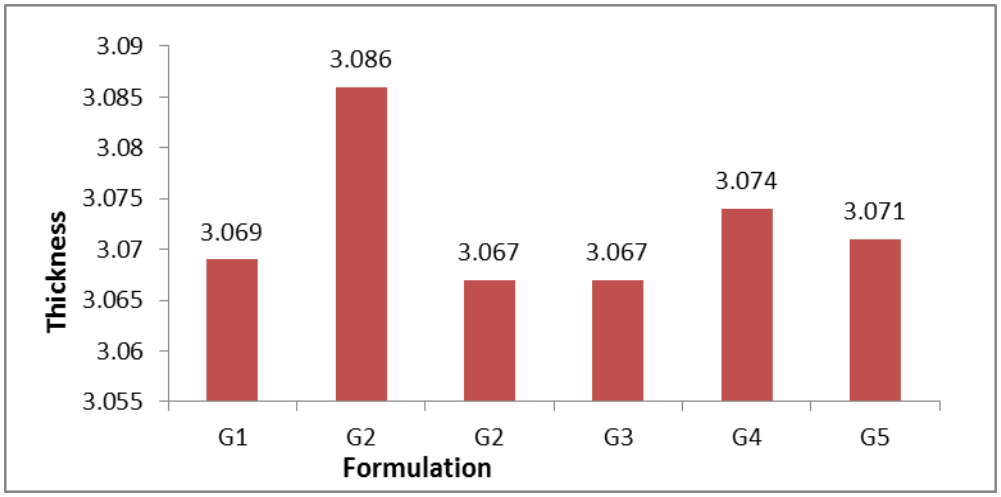

Fig. 8.2: Thickness of prepared formulation of fast dissolving film.

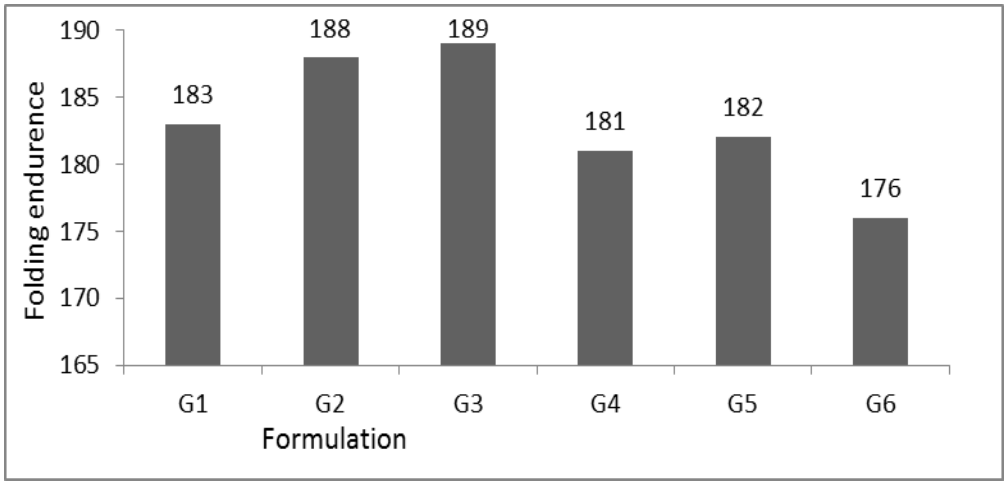

Fig. 8.3: Folding endurance of prepared formulation of fast dissolving film.

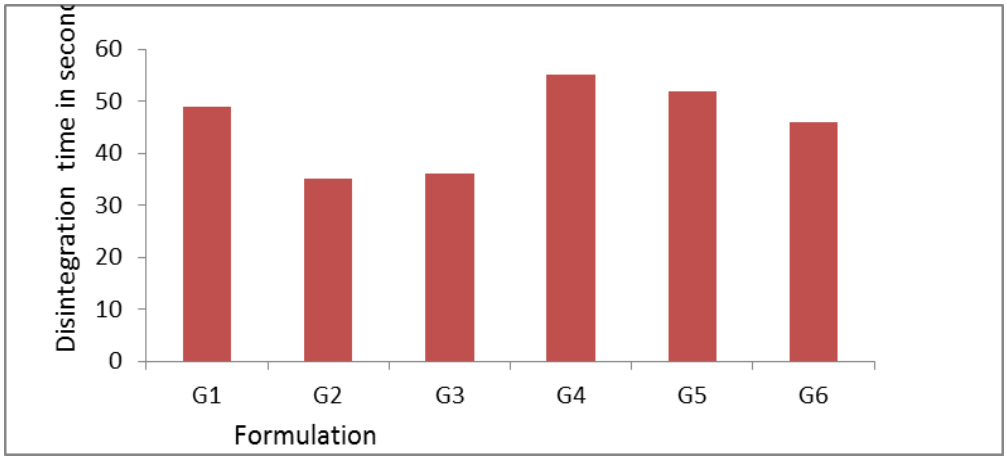

Fig. 8.4: Disintegration time of prepared formulation of fast dissolving film.

Table No.9: Evaluation parameter of film.

Formulation	% Drug content	% Moisture content	Surface pH	Swelling index
G1	0.84	1.08	6.31	0.5
G2	0.98	1.59	6.69	0.6
G3	0.89	1.63	6.55	0.8
G4	0.78	0.54	6.36	0.7
G5	0.75	2.17	6.36	0.4
G6	0.70	1.09	6.41	0.6

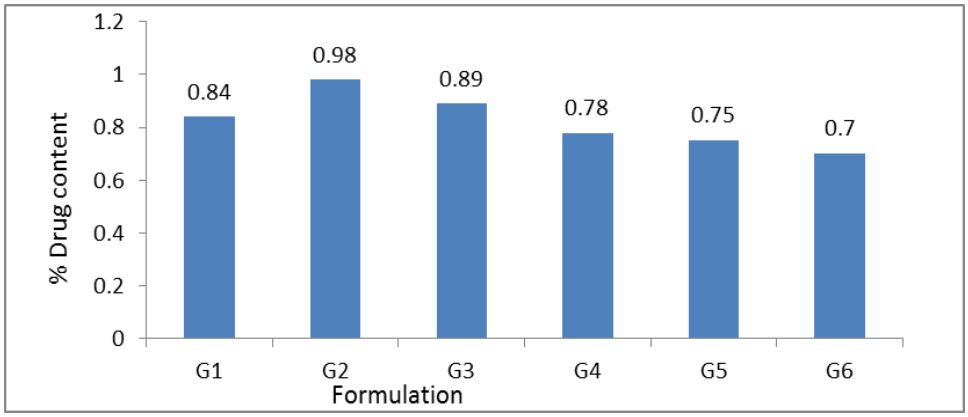

Fig. 9.1: % Drug content of prepared film formulation.

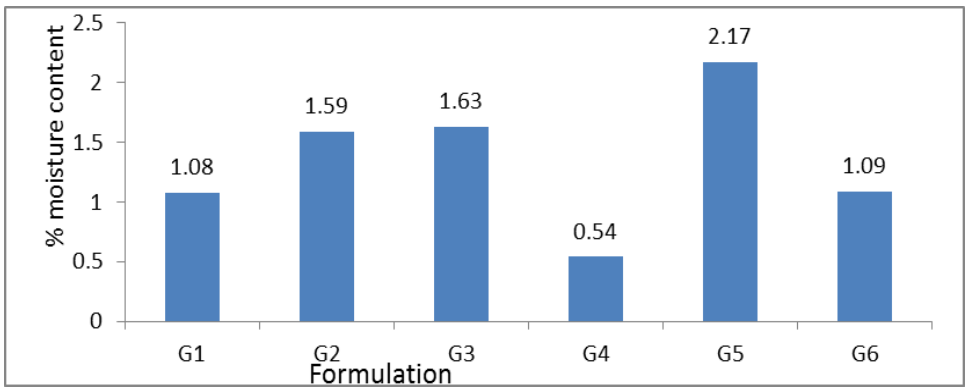

Fig. 9.2: % Moisture content of prepared formulation of film.

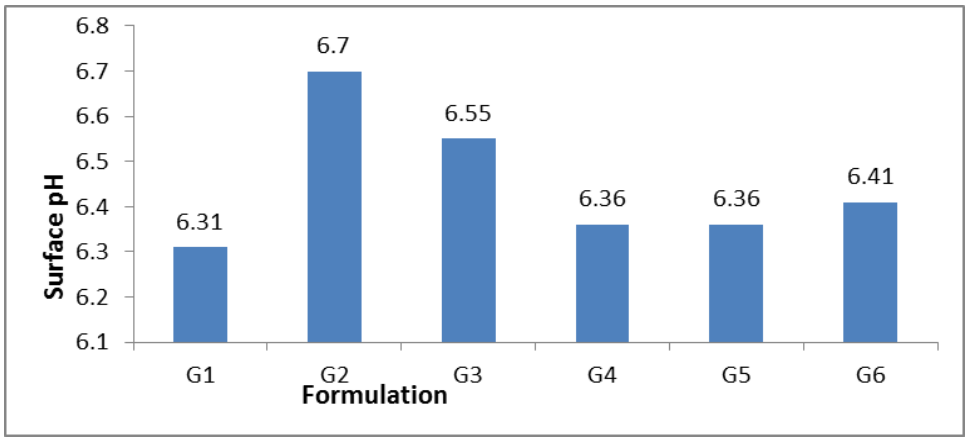

Fig. 9.3: Surface pH of prepared formulation of film.

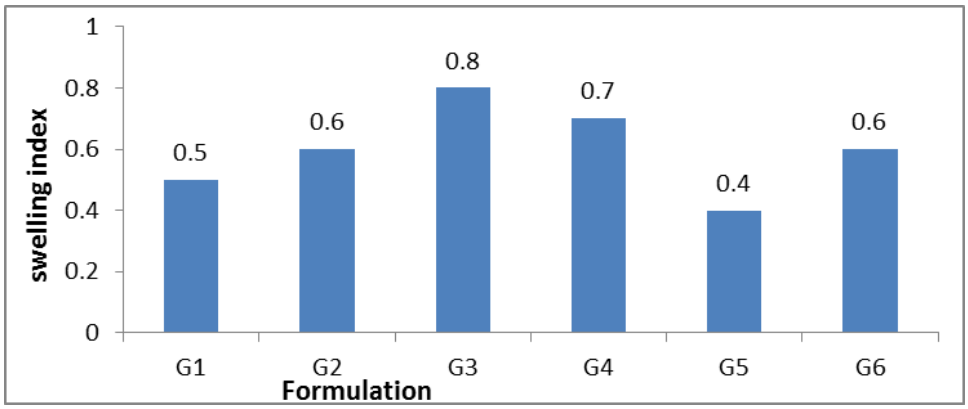

Fig 9.4: swelling index of prepared formulation.

10. IN –VITRO DRUG RELEASE

Table no.10.1: In-vitro drug release in dissolution medium.

FORMULATION							
S.No.	**Time in mint**	**G1**	**G2**	**G3**	**G4**	**G5**	**G6**
1	2	16.84	49.28	40.6	33.08	25.5	20.10
2	4	17.94	68.75	54.70	36.32	38.48	27.67
3	6	25.5	87.13	70.9	41.72	41.72	36.32
4	8	41.72	88.21	80.64	47.13	55.78	42.81
5	10	52.54	90.37	83.89	54.70	68.75	59.02

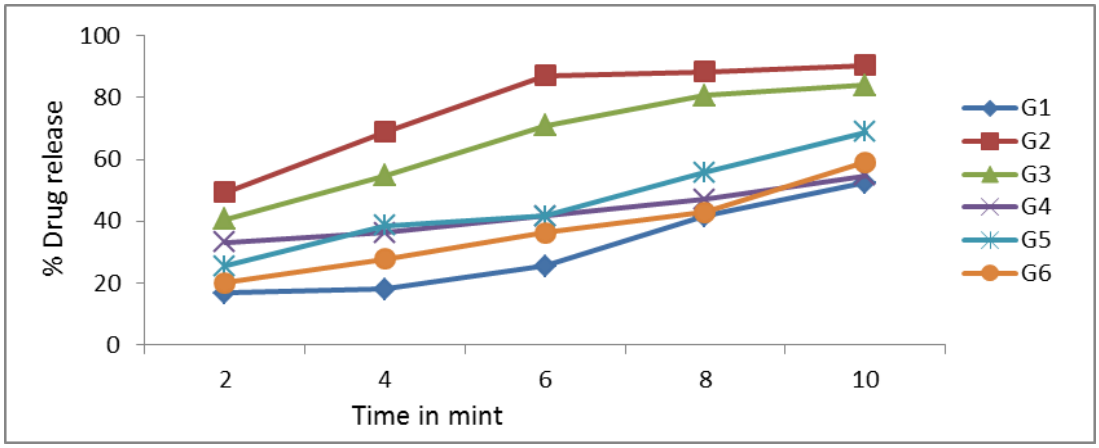

Fig. 10.1: In-vitro drug release of prepared G1,G2,G3,G4,G5,G6 formulations of fast dissolving film.

10.10 In-vitro dissolution drug release study

Table No10.11: In-Vitro Release of The Fast Dissolving Buccal Film.

Formulation	Zero-order (R^2)	First order (R^2)	Higuchi metrix (R^2)	Peppas (R^2)	Hix. Csow (R^2)	Best fit model	Mechanism of release
G1	0.9567	0.9349	0.8958	0.8341	0.9447	Zero order	Anomalous
G2	0.8002	0.9372	0.9584	0.9402	0.9056	Higuchi matrix	Fickion diffusion
G3	0.8866	0.9869	0.9451	0.9878	0.9668	Peppas kormeyer	Fickion diffusion
G4	0.8298	0.8913	0.9511	0.8684	0.8743	Higuchi matrix	Fickion diffusion
G5	0.9525	0.9644	0.9200	0.9599	0.9694	Hixon crowell	Anomalous
G6	0.9667	0.9575	0.9099	0.9605	0.9666	Zero order	Anomalous

Result of correlation coefficient of release data by curve fitting method on zero order, first order, higuchi kinetic, and hixon crowell model and there different exponent. The value of correlation coefficient (r) indicated in the above table respectively.

Table no10.12: % Cumulative Drug Release From G2 buccal film.

Model fiting	**R^2**	**Parameters for Korsmeyer-peppas equation**	
Zero order	0.8002	n	0.3945
1st order	0.9372	k	4.9111
Higuchi matrix	0.9584	Best fit model	Higuchi metrix
peppas	0.9402		
Hix. crow	0.9056	Fickion diffusion (higuchi matrix)	
Mechanism of release			

DISCUSSION

The values of correlation coefficient (r) are indicated in the above table respectively. Upon comparison of correlation coefficient (r) of all the formulations, it was indicated that the release rates follows higuchi metrix, in all case of formulations (G1 to G6). Drug release rate is increase & quick action of formulation having polymer HPMCK15m, beta cyclodextrin and HPMCk4m.

CONCLUSION

Glipizide oral fast acting medicated film was prepared successfully by solvent casting method using various polymers like HPMCK4m, HPMC E15, HPMCK100, β-CYCLODEXTRIN, etc. Drug polymer ratio influences the viscosity of formulation as well as drug release pattern. Oral film are prepared in round shaped and have color transparent to opaque in nature. The optimized formulation showed acceptable physiochemical properties. Percentage drug content was found in all formulation are within 0.89-0.98 and show drug release in rapid manner (higuchi metrix). Formulation G2,G3,G1 show 90.37%, 83.89%, 52.54%, drug release respectively within 10 minutes & similarly formulations G4,G5,G6 have drug release 54.70%, 68.75%, 59.02%.

Formulation G2 (HPMC K4m) shown the highest drug release =90.37% in 10 min which is greatest among all formulation and have clear transparent color. Its pH is found 6.69 and swelling index 0.6mm. Drug content was found to be 0.98%. So the formulation G2 is considered as best formulation among all by above observation.

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