EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 7
Issue: 9
421-440
Year: 2020

FORMULATION AND EVALUATION OF TIMOLOL MALEATE MUCOADHESIVE BUCCAL TABLET AS ANTIHYPERTENSIVE

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Article Received on 18/07/2020 **Article Revised on 07/08/2020** **Article Accepted on 28/08/2020**

ABSTRACT

Back ground: Bioadhesion is simply defined as an ability of material to adhere to a biological tissue for a longer period of time. Mucoadhesion generates the interest in a sequence to enhance localized drug delivery or the delivery of difficult molecule into the systemic circulation. **Objective:** The formulation and evaluation of mucoadhesive buccal tablets containing an antihypertensive drug are related to the ongoing examination such as timolol maleate to overcome the first pass effect and to enhance its bio-availability with the help of reducing in dosing frequency and also dose-related side effects. With the help of changing the concentration of polymers such as carbopol 934, polyethylene oxide and sodium carboxy methyl cellulose, eight formulations will be prepared. **Methods:** Weight variation, hardness, friability, surface pH, drug content uniformity, swelling index, and bioadhesive strength, *in-vitro* drug dissolution study and kinetic studies of the drug release method were used for the tablets testing. FTIR studies exhibited no evidence of interactions between drug, polymers, and excipients. Under sink condition using USP- XXIV dissolution apparatus type 2, *in-vitro* drug release study of timolol maleate was performed. **Results:** The *in-vitro* drug release achieved with the formulation F1 was efficient, which contain the drug, carbopol 934p and polyethylene oxide in the ratio of 1:3:9.5. The result of formulation F1 was found to be surface pH (6.35), bioadhesive strength (36.5 gm) and (82.2 %) swelling index. **Conclusion:** The tablets (formulation F1) containing 10 mg of timolol maleate exhibited drug release such as 98.36% with desired therapeutic concentration. The dissolution studies of all formulations data were found to be zero-order drug release kinetics.

KEYWORDS: Timolol maleate, Carbopol 934, Polyethylene oxide, Sodium Carboxy Methyl Cellulose, Mucoadhesive, Antihypertensive.

1.1. INTRODUCTION

1.2 Bioadhesion and mucoadhesion

Adhesion, is defined as the contact bond between a pressure-sensitive adhesive (such as glue, mucilage, or paste) and a surface. The term 'bioadhesion' simply defined as the state of two materials, partially first is of biological in terms of nature, are together maintained for a longer time with the interfacial forces. Bioadhesion is simply defined as the capability of material to get adhered to tissue of biological nature for a substantial time.[1, 2]

a) Cell adhesion on a silicon-based micropillar array.
b) Examples of medical application where fibrin glue was attach a surgical mesh after a laparoscopic surgery procedure.
c) Tooth enamel and dentin fracture and reattachment of tooth fragments using a dentin adhesive.
d) Adhesion of a mussel on glass slide, where threads composed of the mussel adhesive protein were secreted by the animal to attach itself to the glass surface.[3]
e) Sketch depicting fat deposition on a blood vessel wall in atherosclerosis as shown in **Fig. 1**.

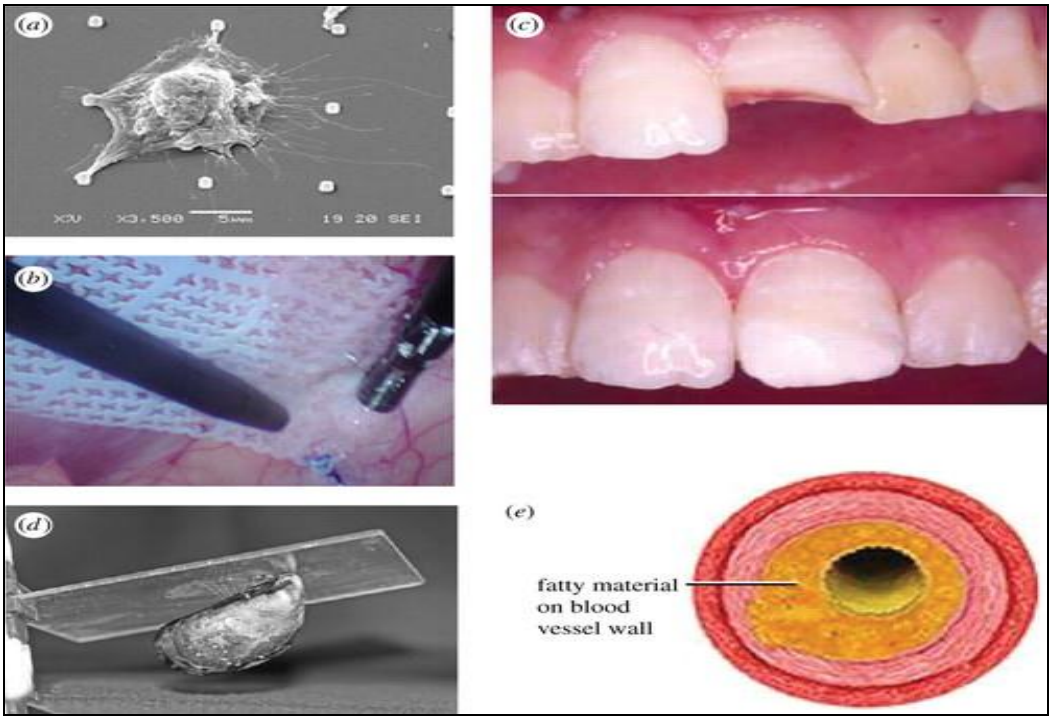

Fig. 1: Example of bioadhesion.

"Mucous membrane" is said as the special site for bio-adhesive science, though the necessity for new "bio adhesive formulations" for the administrations to the dermal pathway has been explored when a cutaneous action for prolonged interval was desired. Mucous membranes of animal and man are relatively permissible and allow the fast absorption of medicine. They are characterized by the "epithelial cells "whose surface is mostly covered by mucus. The mucus are mainly contains lipids, glycoproteins, 95% of the water by mass and inorganic salts that make it a system of hydration activity.

Mucin an important mucus glycoprotein is responsible for the type of structure it possesses. The two robust role of mucus are protection and lubrication of the epithelium layer. The thickness is variable that is ranging from 50-450 µm in the gastro part whereas in the oral cavity it is less than 1 µm. The other mucus routes apart from GI, involve the buccal, nasal, oral, rectal, and periodontal have also been studied. The term "Mucoadhesion" is used in case of polymer get attached to the mucin layer of a mucus forming cell. When the biological substrate is mucous membrane then the phenomenon is known as "mucoadhesion". Bio-adhesive systems mainly applicable on the mucous membrane are frequently defined as mucoadhesive, but the terms are interchangeable.[4]

Mucoadhesion is observed where two surfaces are present and one of which is the mucous membrane, and the other adheres to the counterpart. Therefore, there are already conventional drug delivery systems in place that are bioadhesive after a redesigning approach by the inclusion of the "bioadhesive substances" in their respective formulations.[5]

There are a numerous materials used for the development of that systems. Some drastically studied materials are those polymers that are derived from the polyacrylic acids, like polycarbophil, polyethylene oxide polymers that are incredibly derived from cellulose, such as sodium carboxymethyl cellulose, and the hydroxyethyl cellulose.[6]

Mucoadhesiongene rates the interest in a sequence to accelerate the localized drug delivery or the delivery of the molecule into the systemic circulation.[7]

The mechanism by which mucoadhesion takes place has been said to have two stages, the contact stage and the consolidation stage as shown in **Fig. 2**, Initial stage is characterized by the contact between the mucoadhesive and the mucous membrane which is then followed with the swelling and spreading of the formulation. It initiates its deep contact with the mucus layer.[8]

In the consolidation step (**Fig.1 & 2**), the mucoadhesive materials are activated by the presence of moisture. The system get plasticized with the moisture, breaking the mucoadhesive molecules and linked them up by weak Van der Waals and hydrogen bonds.[9]

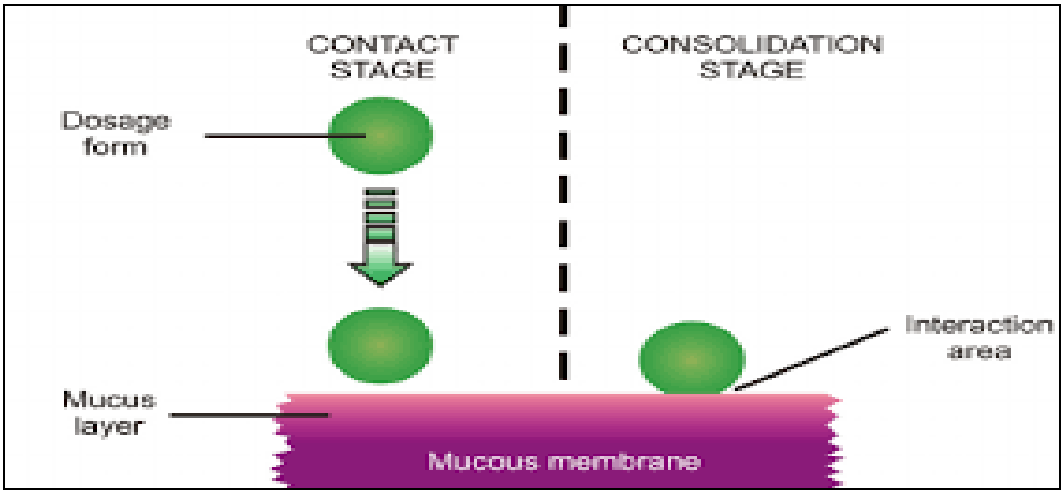

Fig. 2: The two steps of the mucoadhesion process.

Therefore, it is the water motion that leads to the consolidation of the adhesive bond, and not the interpenetration of macro molecular chains. So, the dehydration theory as shown in **Fig. 3** is not applicable to solid formulations or highly hydrated forms. [10, 11]

Since the early 1980s, "oral delivery" of the necessary drug viamucoadhesive polymer has been the study of interest. Buccal delivery simply defined as the administration of the drug via the mucosal membrane of the oral cavity. The mucosal lining present in buccal tissue have some advantages e.g. it is highly vascularized, the administration and removal accessibility of the dosage form, acceptability of patient when compared to other non-oral routes. It prevents the acid hydrolysis in the GI and reduces the metabolism via liver.

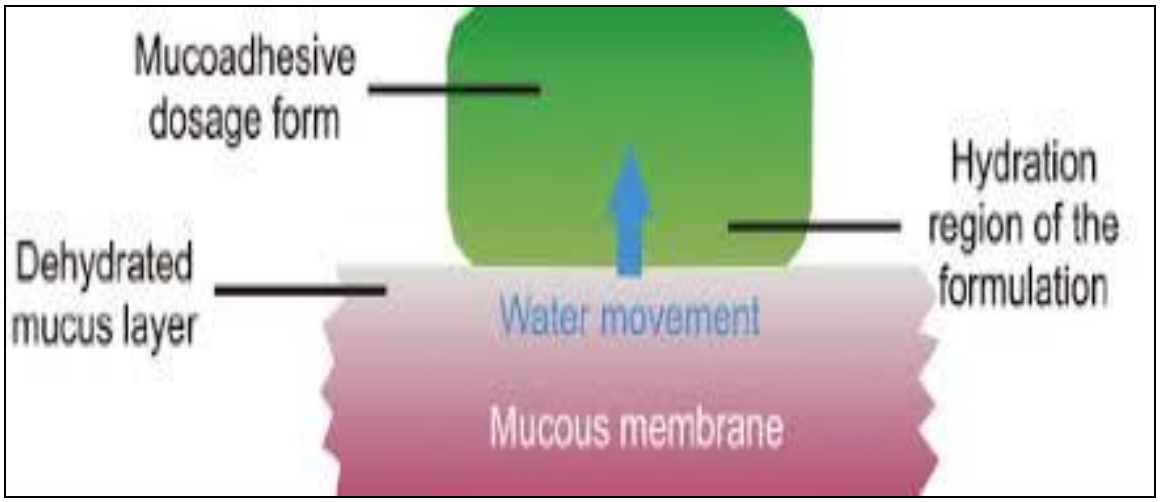

Fig. 3: Dehydration theory of mucoadhesion.

In our study we are trying to develop a formulation with mucoadhesion capable of delivering the selected anti-diabetic drug in the therapeutic concentration of suitable choice for longer duration of time. Following polymers are used in a different ratio to formulate mucoadhesive buccal tablet, which provides good mucoadhesion property and sustained release of a drug product in systemic circulation.[12]

"Bioadhesion" is an ability of adhesion through a material to a specified region for the sufficient period of time that is not only intended for local drug targeting but better control of systemically drug delivery. The challenges faced by the first-pass metabolism and degradation of medicine in the harsh gastro-intestinal area can be solved by the administration of the drug to the route of oral. In some cases of the oral cavity, the self medication is easily accessible. The medication is terminated in the bad cases by removing the bucco-adhesive patch.

This dosage form has made it possible to administer those drugs to patients who are not dosed orally. The oral mucosa is a very useful site for the drug delivery to the systemic circulation in the recent years. A drug through the buccal mucosa enters directly into the circulation systemically and get via the reduced first pass metabolism and the adverse gastrointestinal effect. Oral

mucosa is used as the appropriate choice of the site when the drug delivery of prolonged version is desired. The oral site is lesser permeable than sublingual.[13]

1.3 Mucoadhesion Theory

As we know that the chemical and physical based mucoadhesion are not still well understand by anyone. At present, the classical theories got adapted from studies of the several materials and polymer-polymer adhesion.[14]

1.4 Hypertension

Hypertension is the chronic disease characterized by elevation of blood pressure. It is noted with the high BP above the 120/80 for the systolic and diastolic mm Hg in the artery. Generally the mean arterial pressure of >110 mm Hg under the normal conditions is considered to be hypertensive; this normally occur when the diastolic BP is >90 mm Hg and the systolic blood pressure is about >135-140 mm Hg. Hypertension increases the risk of various other cardiovascular diseases like heart attack, stroke and non-cardiovascular diseases like end stage of renal failure, renal damage etc.

Table 1: Types of hypertension.

Category pressure	Systolic pressure (mmHg)	Diastolic pressure of (mm Hg)
Normal	90-110	60-78
Pre-hypertension	120-130	80-88
Stage-1	140-150	90-100
Stage-2	≥110	≥90
Isolated systolic hypertension	≥110	<90

2.1. MATERIAL AND METHODS

2.2 Materials: Timolol maleate was a gift sample from R. P. Pharmaceuticals, Kanpur. Polyethylene oxide, carbopol 934, sodium carboxy methyl cellulose was gift sample from Lloyd College of Pharmacy, Greater Noida. All other reagents used were of analytical grade which is present in the College Lloyd College of Pharmacy, Greater Noida, India. Other materials: mannitol, magnesium stearate, talc etc.

2.3 Equipments: Electronic balance, pH meter, FTIR spectrophotometer, melting point apparatus, hot air oven, water bath shaker, magnetic stirrer, tablet punching machine.

2.4 Methodology: The drug (timolol maleate), polymers (carbopol 934p, polyethylene oxide, sodium CMC) and excipients were mixed homogeneously in a glass mortar for 15 min. The mixture was compressed using an 8 mm, biconcave punch in a single-stroke by using the 8-station rotary machine (The Rimek Mini Press-1) and 150mg tablets were formed.

3.1. RESULTS AND DISCUSSION

The current research work was concerned with the formulation and evaluation of timolol maleate mucoadhesive buccal tablet by using 03 different mucoadhesive polymers polyethylene oxide, carbopol 934, sodium carboxy methyl cellulose with varying concentrations by using direct compression method.

3.2 The infrared spectra of pure drug

Timolol and the mixture of polymer and excipients were studied by FTIR spectroscopy using suitable solvent KBR. The data are presented in the **Fig. 4, 5, 6 & 7**. From the results it was evident that there is no chemical incompatibility between drug-excipients, drug-polymer, and polymer-excipients.

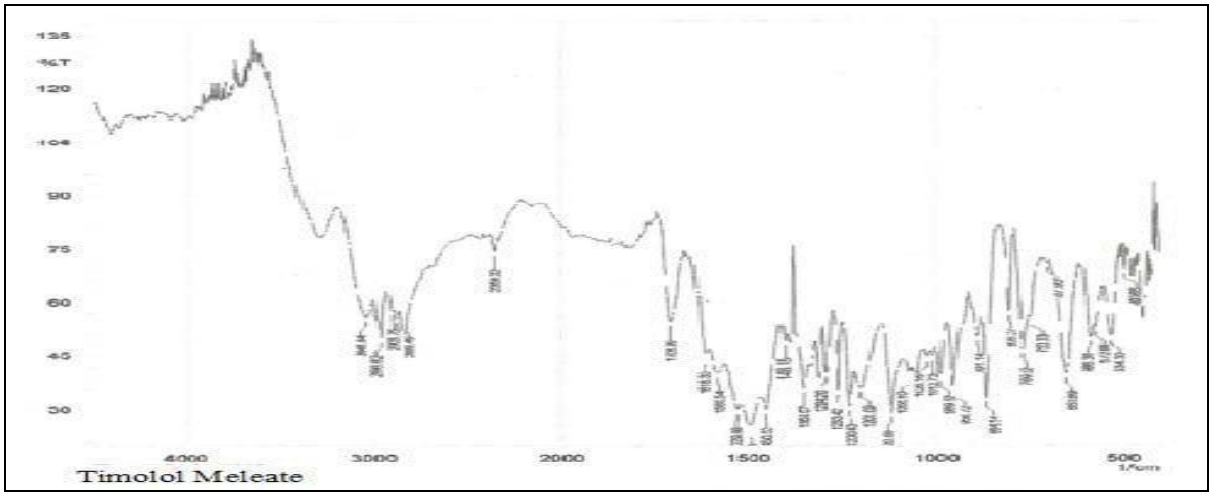

Fig.4: FTIR of timolol maleate.

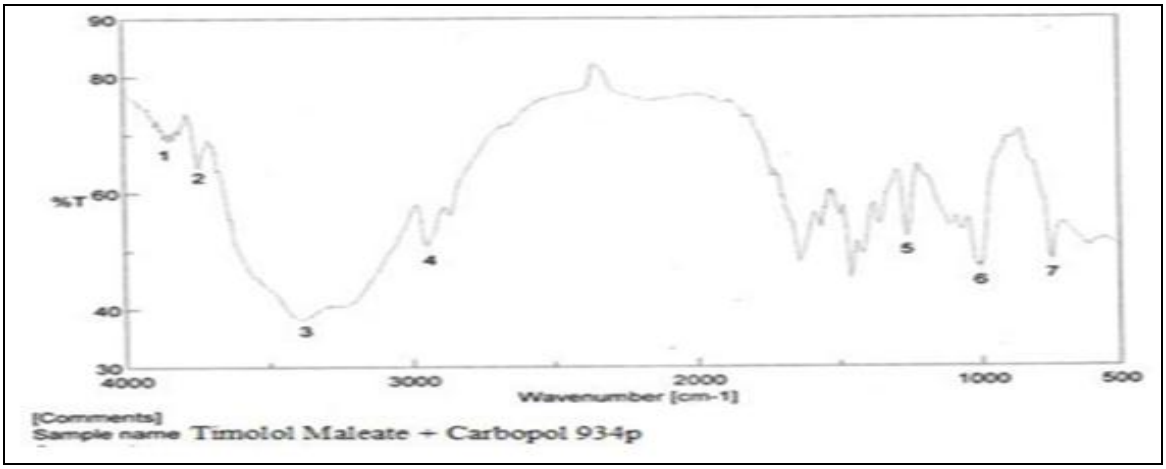

Fig. 5: FTIR of timolol maleate & carbopol 934p.

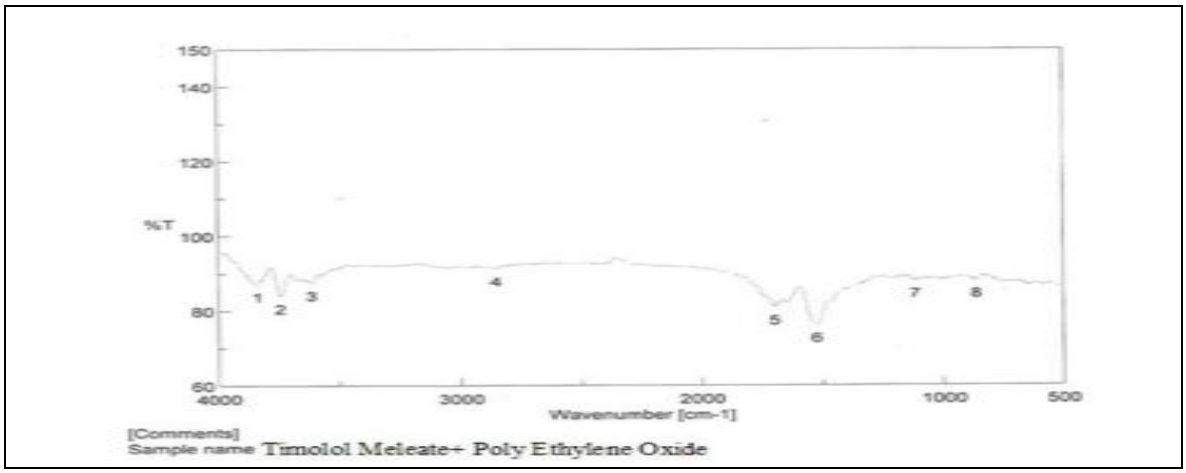

Fig. 6: FTIR of timolol maleate & polyethylene oxide.

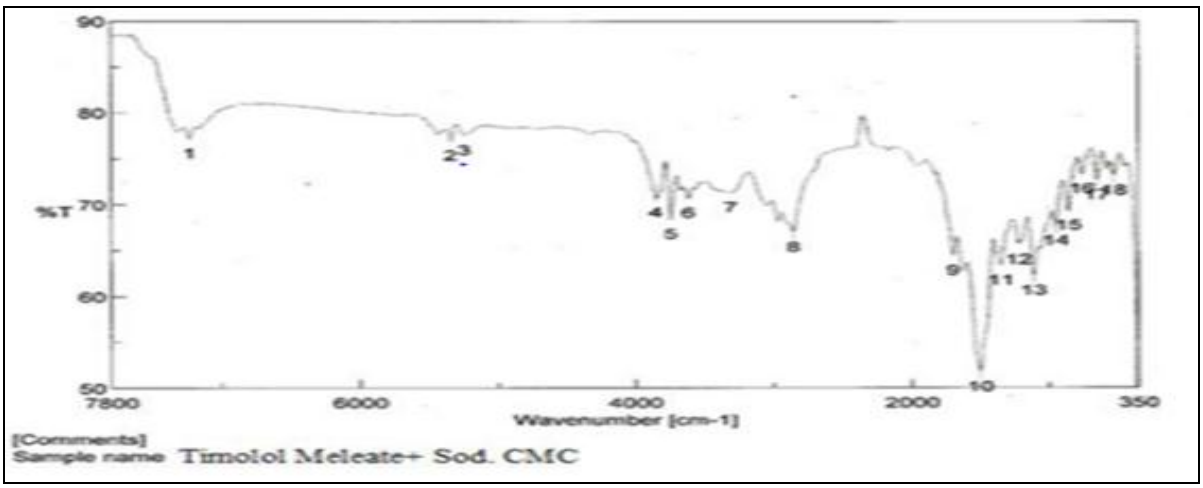

Fig. 7: FTIR of timolol maleate & sod CMC.

3.3 Precompression Properties The precompression properties (physical) of powder blend were evaluated *e.g.* angle of repose, tapped density, bulk density, compressibility index and Hausner ratio. The angle of repose was found to be in between 30˚ and 32˚. This indicates that passable flowability. The percentage compressibility index and Hausner ratio were found to be (<15%).

3.4 Evaluation Parameters: The eight different formulations of timolol buccal tablets were prepared, in order to select the best formulation. Different evaluation parameters were checked and subjected to *in-vitro* dissolution test and their release properties were observed.

3.5 Weight variation test: The weight variation test was conducted for each batch of all formulations F1 to F8 as per I.P. and the results are shown in **Table 2** & **Fig. 8**. All the tablets passed weight variation test. None of the formulations showed deviation (I.P. Limit ± 10%) for any tablet tested.

Table 2: Weight variation, hardness, and friability of timolol buccal formulations.

Formulation Code	Average Weight of Tablet (mg)	Hardness (Kg/Cm^2)	Friability (%)
F1	148.97±0.03	3.7±0.28	0.33±0.08
F2	150.01±0.02	7.4±0.25	0.53±0.05
F3	149.65±0.05	5.7±0.19	0.57±0.09
F4	148.87±0.08	6.7±0.23	0.67±0.05
F5	151.57±0.03	4.7±0.50	0.77±0.07
F6	149.90±0.02	3.3±0.23	0.37±0.03
F7	149.51±0.07	5.2±0.18	0.47±0.06
F8	148.87±0.03	4.7±0.17	0.50±0.04

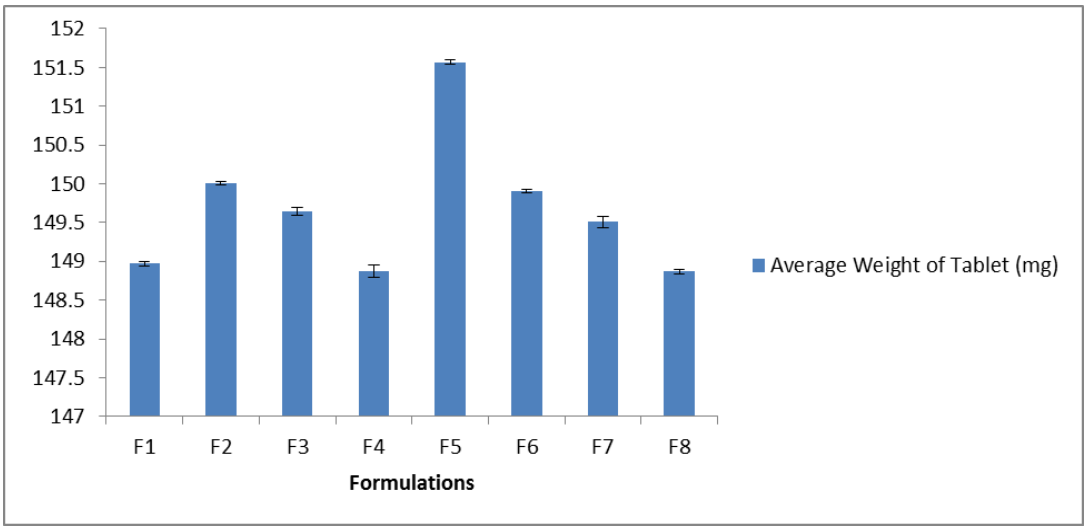

Fig. 8: Weight variations in timolol tablets.

3.6 Hardness test: The tablet hardness is necessary for consumer acceptance and handling. The measured hardness of the tablets of each batch of all formulations such as F1 to F8 was ranged between 3.1 to 7.2 kg/cm^2 and the results are shown in **Table 2**, **Fig. 9**. This sure that is good handling.

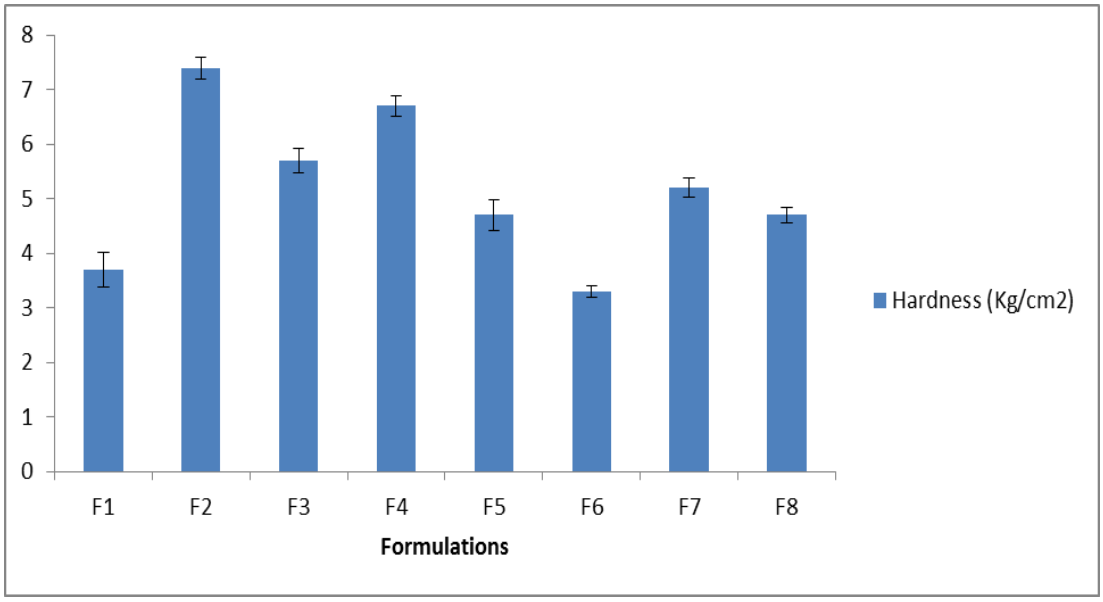

Fig. 9: Hardness of timolol tablets.

3.7 Friability test: The friability test for all the formulations was done as per the standard procedure I.P. and the results of the friability test were tabulated in **Table 2**, **Fig 10**. The data indicate that the friability was less than 1% in all formulations ensuring that the tablets were automatically stable.

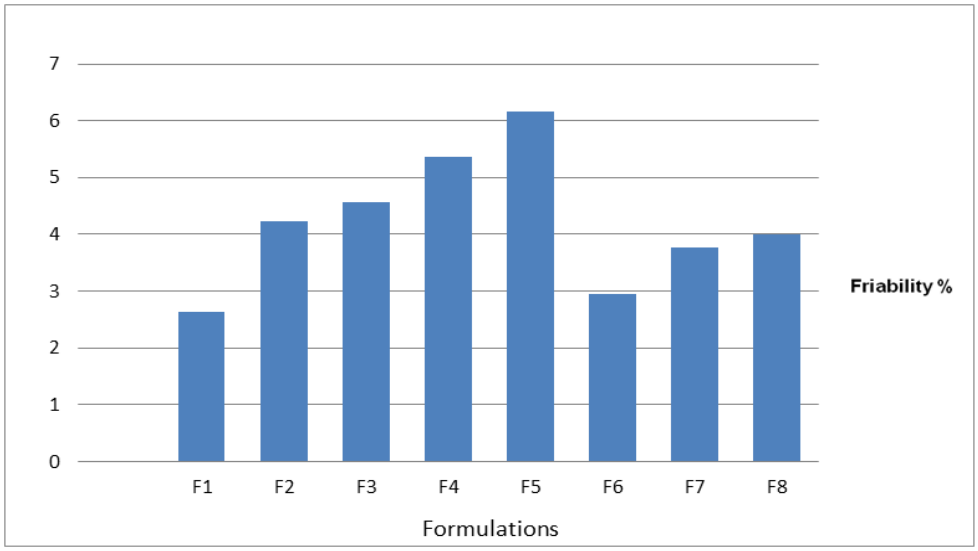

Fig. 10: friability of timolol tablets (%).

3.8 Thickness: The thickness of the tablets was found to be reliable in all formulations F1 to F8. The thickness was found to be in the range of 2.3 to 2.8 mm. None of the formulations (F1 to F8) showed a deviation. Hence, it is concluded that all the formulations complied with the thickness test and the results are shown in **Table 3, Fig. 11**.

Table 3: Thickness, drug content (in %), surface pH and bioadhesive strength of timolol buccal tablets (formulations F1 to F8).

Formulation code	Thickness (in mm)	Drug content (in %)	Surface pH	Bioadhesive strength (in gm)
F1	2.8±0.32	98.04±0.035	6.34±0.038	36.4±0.02
F2	2.3±0.20	99.81±0.015	6.33±0.026	33.4±0.04
F3	2.6±0.23	99.13±0.032	6.22±0.023	34.1±0.08
F4	2.4±0.18	96.51±0.028	6.65±0.025	31.4±0.03
F5	2.7±0.28	94.61±0.039	5.77±0.018	31.3±0.05
F6	2.6±0.11	98.26±0.029	6.17±0.023	27.5±0.06
F7	2.8±0.17	97.88±0.032	6.01±0.051	29.4±0.04
F8	2.5±0.15	96.56±0.038	5.79±0.035	31.4±0.07

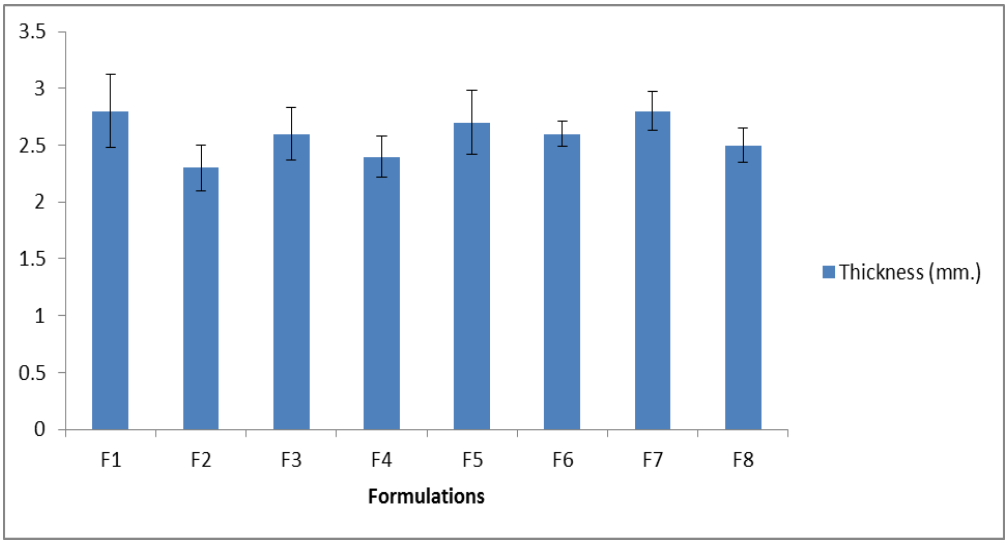

Fig. 11: Thickness of timolol tablets.

3.9 Drug content: The drug content of each batch of all the formulations (F1 to F8) was evaluated as per the standard protocol and the results are shown in **Table 3, Fig.12**. The results indicate that the percentage of drug content was found to be in between 94.61% to 99.81%. Hence it is concluded that all the formulations are following acceptable limits as per I.P. such as ± 5%.

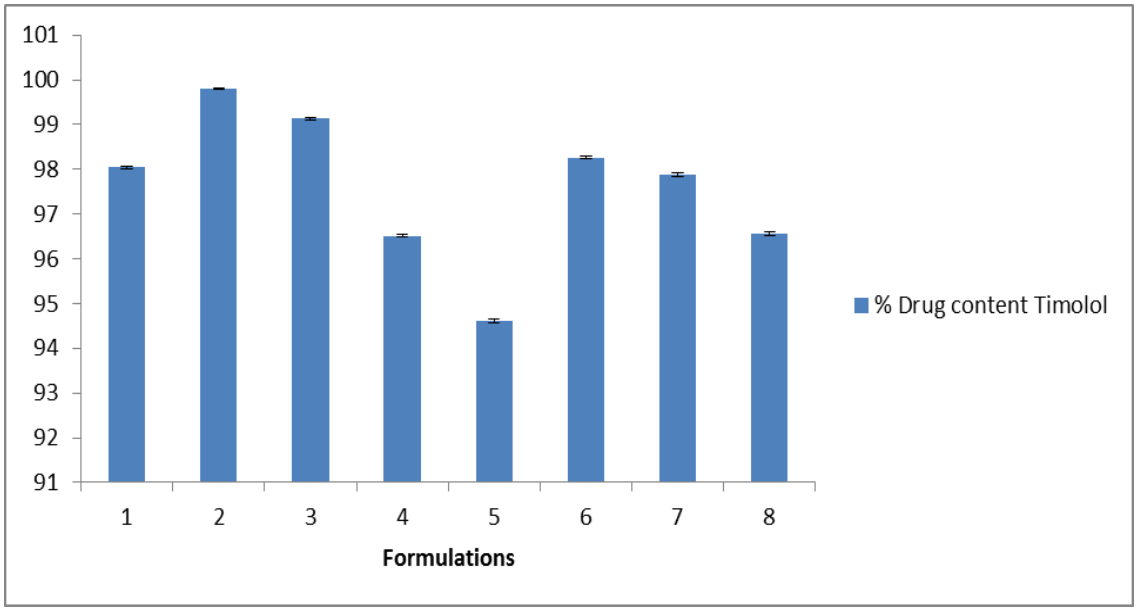

Fig. 12: Percent drug content in timolol tablets.

3.10 Surface pH: Surface pH of all the formulations F1 to F8 was found to be 5.77 to 6.65. The acceptable pH of saliva is in the range 5.5 to 7.0. Hence, it was concluded that all the formulations may not produce any local irritation to the mucosal surface and the results are in **Table 3, Fig.13**.

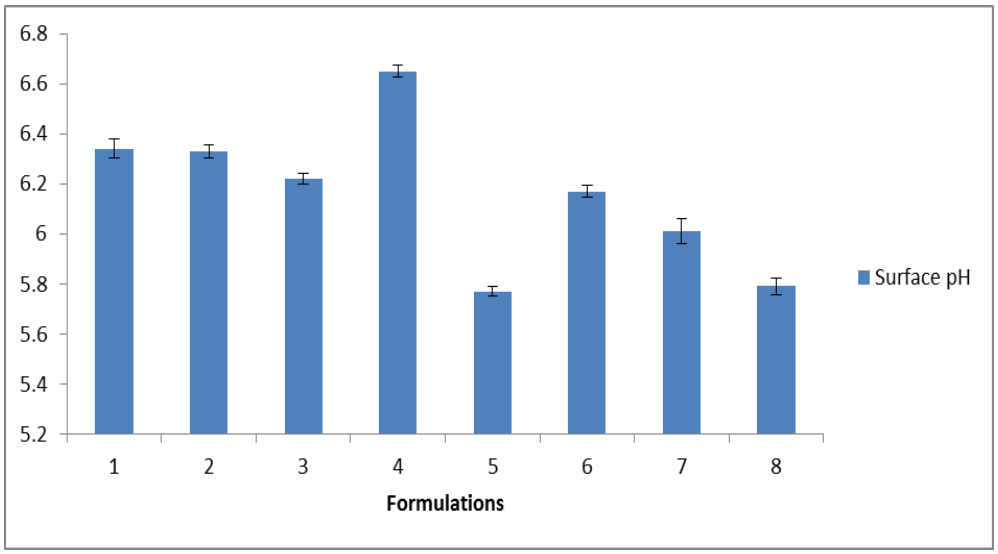

Fig. 13: Surface pH of timolol tablets.

3.11 Bioadhesive strength: The *in-vitro* bioadhesive strength study was performed and the results are shown in **Table 3**. On the modified physical balance and measure the force (N) required detaching the tablet. The adhesion characteristics were affected by the conc. of the bioadhesive polymers. Increase in conc. of polymer increases bioadhesive strength of formulation. The formulations (F1, F2, F3 & F4) with carbopol 934p and polyethylene oxide (PEO) showed the bioadhesive strengths of 36.4gm, 33.4gm, 34.1gm and 31.4gm respectively. The formulations (F5, F6, F7 & F8) with carbopol 934p and sod CMC showed the bioadhesive strengths of 31.3gm, 27.5gm, 29.4gm and 31.4gm respectively in **Table 3, Fig 14.**

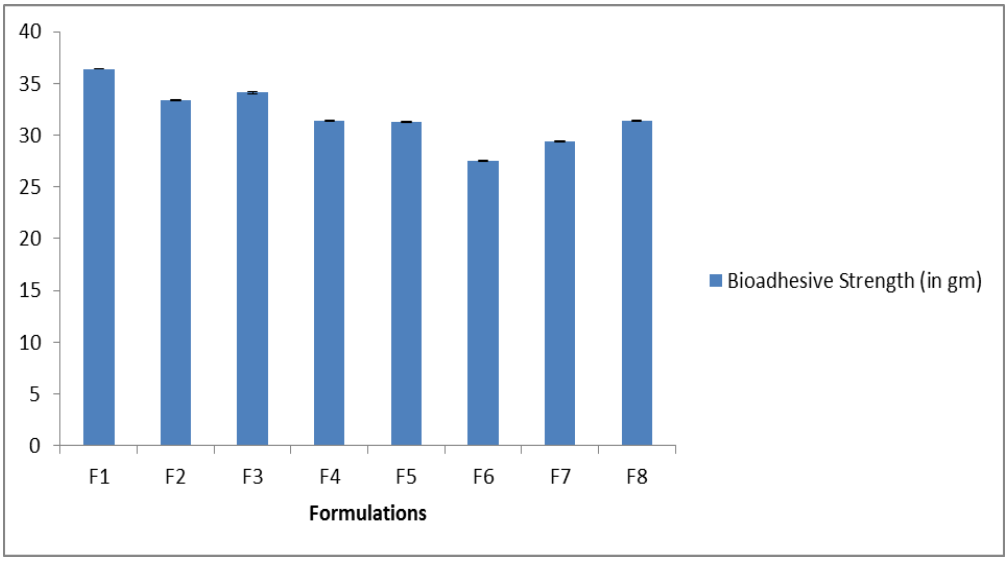

Fig. 14: Bioadhesive strength of timolol buccal tablets.

3.12 Swelling study: The swelling study conducted in all formulations *i.e.* F1 to F8. All the results were shown in **Table 4**. All the formulations were hydrated generally by keeping the tablets in contact with water for 1 hr to 8 hr. The highest hydration (swelling) *i.e.* 82.3% was observed with the formulation F1. This may be due to quick hydration of polymers (carbopol 934P and polyethylene oxide). The swelling rate of tablets increased in the case of formulation F1 containing carbopol 934p and Polyethylene oxide in the ratio of 1:3:9.5. **Table 4 and Fig.15.**

Table 4: Percentage of hydration of timolol buccal tablet formulations.

Formulation Code	1 hrs (%)	2hrs (%)	4hrs (%)	6hrs (%)	8hrs (%)
F1	49.0	63.6	72.4	77.5	82.3
F2	47.1	50.1	61.7	65.4	74.5
F3	47.4	48.5	53.4	59.7	66.1
F4	38.5	55.6	60.1	64.3	71.4
F5	45.0	56.1	61.3	66.0	69.0
F6	39.1	50.1	54.6	61.6	74.3
F7	41.1	50.4	58.4	69.6	71.2
F8	39.8	47.2	55.1	61.4	69.4

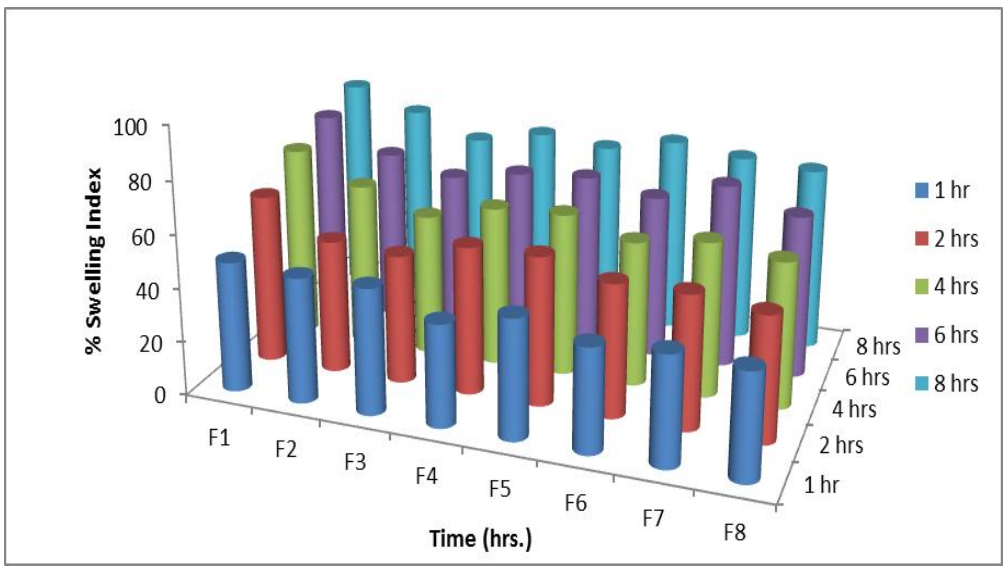

Fig. 15: Percentage of hydration of timolol buccal tablets.

3.13 *In-vitro* Dissolution Study *In-vitro* drug release data of formulation F1 to F8 were suitable to zero order, first order equations to ascertain the pattern of drug release was given in **tables 5 -13**. The R-value was found

to be higher in zero-order followed by first order equation which indicates that all the formulations followed the zero order release pattern. An *in-vitro* dissolution study was designed to carry out in such a way that they mimic *in-vivo* conditions. For *in-vitro* dissolution study, it was confirmed to carry out the dissolution in pH 6.8 phosphate buffer. The data are shown in **Fig.16**.

The formulations F1, F2, F3 & F4 containing drug, carbopol 934p and polyethylene oxide (PEO) polymers in the ratios of 1:3:9.5, 1:4:8.5, 1:5:7.5 and 1:6:6.5 respectively. The *in-vitro* cumulative drug release profile of formulations F1, F2, F3, and F4 showed 98.36%, 96.90%, 93.36% and 94.64% respectively. Among these four formulations, F1 was found to be highest percentage drug release. During the study, it was observed that the tablets were initially swelled and no erodible over the period of 7 hrs.

Similarly the formulations F5, F6, F7 & F8 containing drug, carbopol 934p and sod CMC polymers in the ratios of 1:3:9.5, 1:4:8.5, 1:5:7.5 and 1:6:6.5 respectively. The *In-vitro* drug release profile of formulations F5, F6, F7, and F8 showed 90.10%, 89.15%, 88.25% and 89.5% respectively. Among these four formulations, F5 was found to be highest percentage drug release. During the study, it was observed that the tablets were initially swelled and no erodible over the period of 7 hrs. So here, It was concluded that if formulation containing poly-ethylene oxide polymer was replaced by the formulation containing sodium CMC polymer, then the ratio of formulation F5 showed minimum drug release in comparison to the formulation 1 containing ratio 1:3:9.5. So here, we can say that the formulation F1 *in-vitro* release found to be maximum.

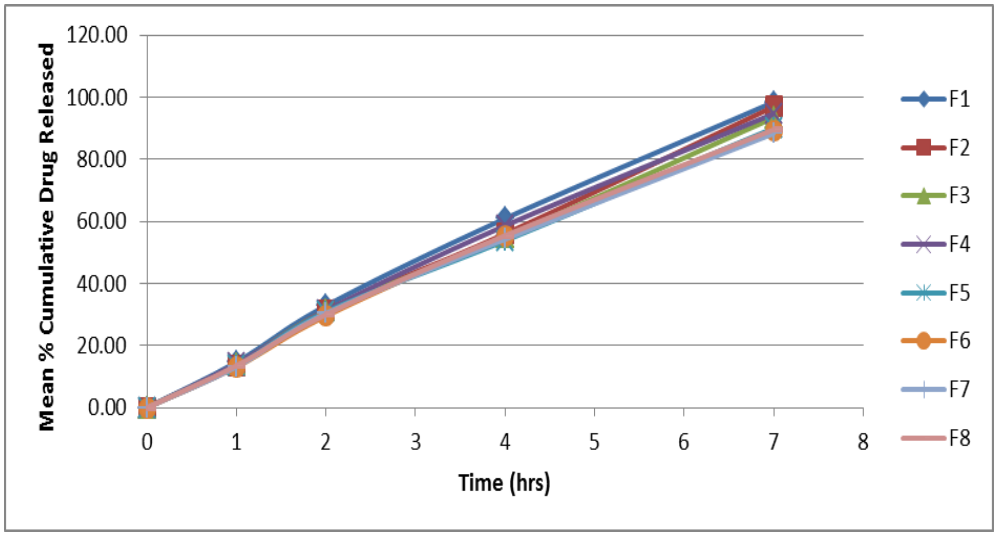

Fig. 16: Mean percent cumulative drug release from timolol formulations.

3.14 Drug release kinetics: *In-vitro* drug release data for all the formulations F1 to F8 were subjected to release kinetic study according to zero order kinetics ascertain the mechanism of drug release. So, all the formulations followed zero-order kinetics. The R^2 values were found to be higher in zero- order kinetics.

Table 5: Release kinetics of F1.

S. No	Time (hrs)	%Cumulative Drug Release	Square root of time	Log time	Log %cumulative drug release	%cumulative drug remained	Log %cumulative drug remained	Cube root of % Drug Remaining
1	0	0	0	0	0	100	2	4.642
2	1	14.64	1	0	1.166	85.36	1.931	4.403
3	2	32.79	1.414	0.301	1.516	67.21	1.827	4.066
4	4	60.89	2.000	0.602	1.785	39.11	1.592	3.394
5	7	98.4	2.646	0.845	1.993	1.6	0.204	1.170

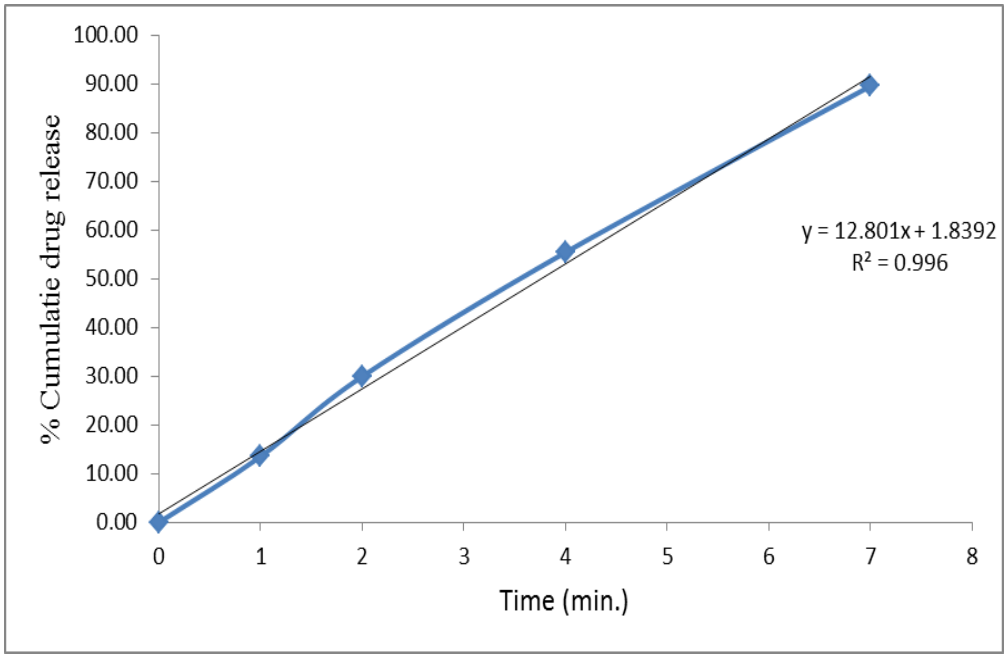

Fig. 17: Zero order model for formulation F1.

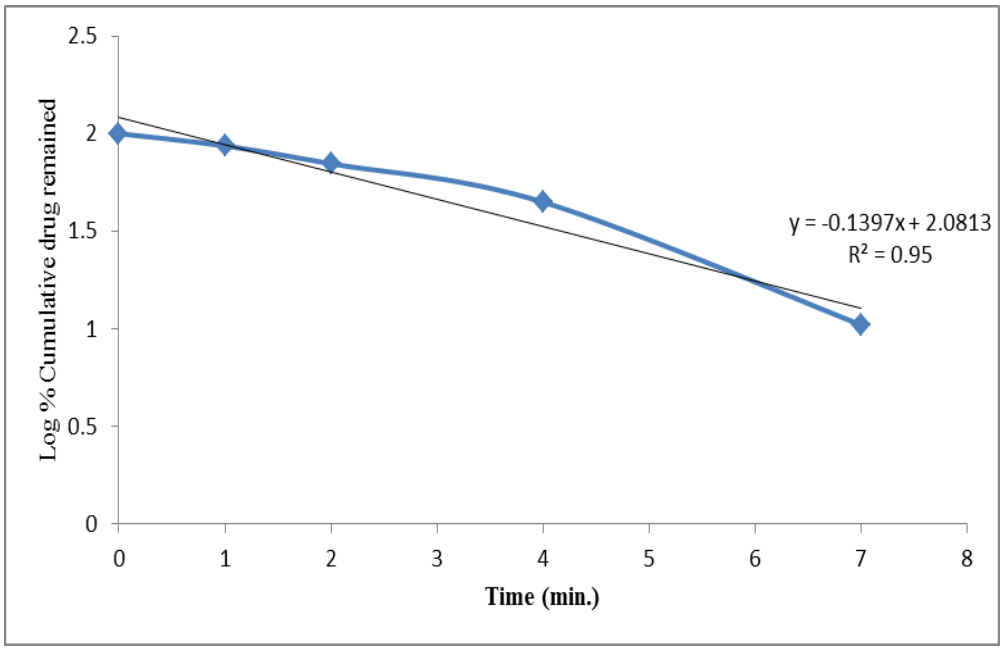

Fig. 18: First order model for formulation F1.

Table 6: Release kinetics of F2.

S.No	Time(hrs)	% Cumulative Drug Release	Square root of time	Log time	Log %cumulative drug release	%cumulative drug remained	Log %cumulative drug remained	Cube root of % Drug Remaining
1	**0**	0.00	0	0	0	100	2	4.642
2	**1**	13.42	1	0	1.128	86.58	1.937	4.424
3	**2**	31.30	1.414	0.301	1.496	68.7	1.837	4.096
4	**4**	55.99	2.000	0.602	1.748	44.014	1.644	3.531
5	**7**	96.94	2.646	0.845	1.987	3.06	0.486	1.452

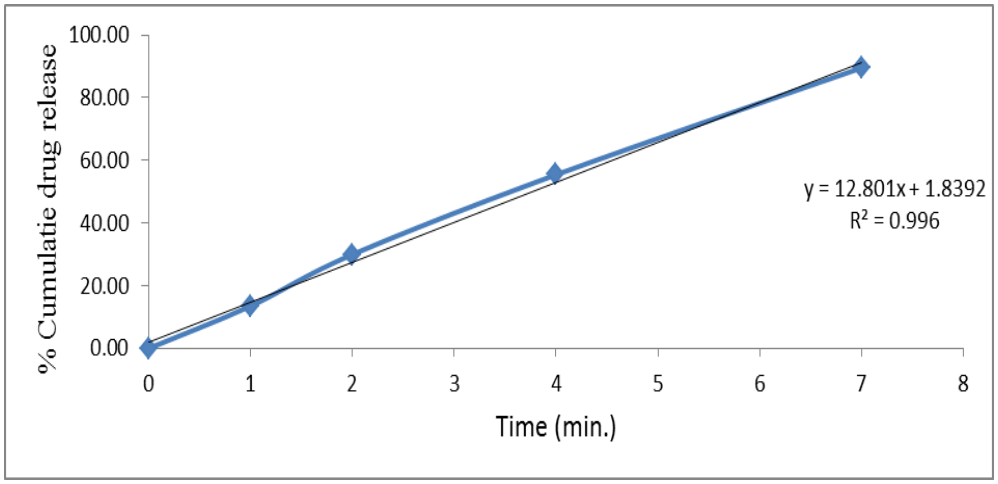

Fig. 19: Zero order model for formulation F2.

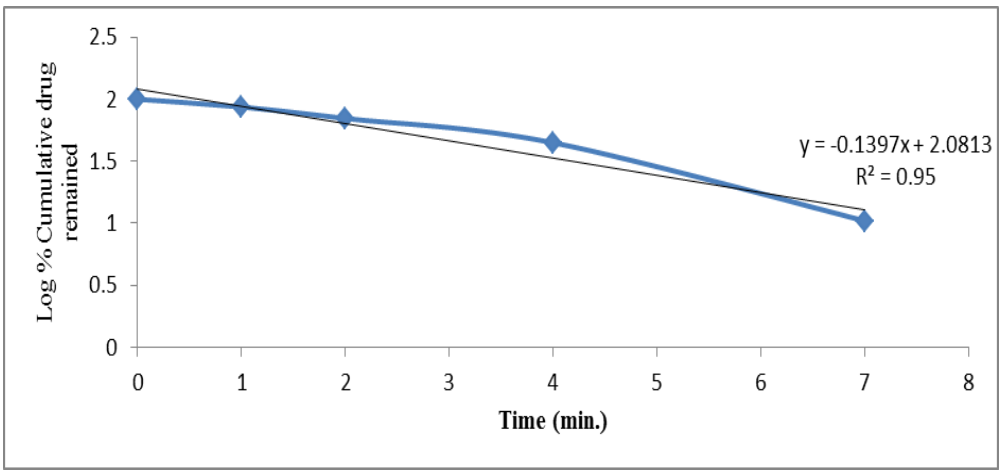

Fig. 20: First order model for formulation F2.

Table 7: Release kinetics of F3.

S. No	Time(hrs)	%Cumulative Drug Release	Square root of time	Log time	Log %cumulative drug release	%cumulative drug remained	Log %cumulative drug remained	Cube root of % Drug Remaining
1	0	0.00	0	0	0	100	2	4.642
2	1	13.89	1	0	1.143	86.10	1.935	4.416
3	2	31.12	1.414	0.301	1.493	68.88	1.838	4.099
4	4	54.79	2.000	0.602	1.739	45.20	1.655	3.562
5	7	93.40	2.646	0.845	1.970	6.6	0.820	1.876

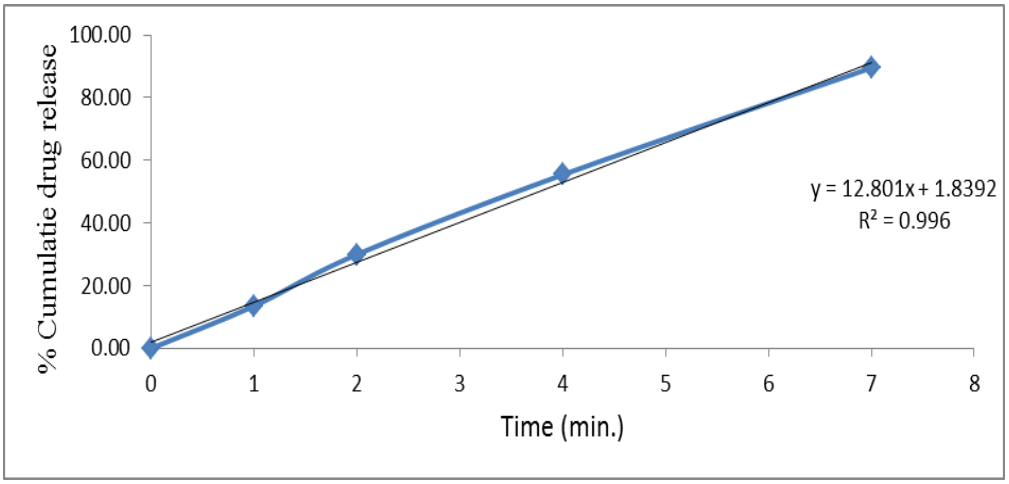

Fig. 21: Zero order model for formulation F3.

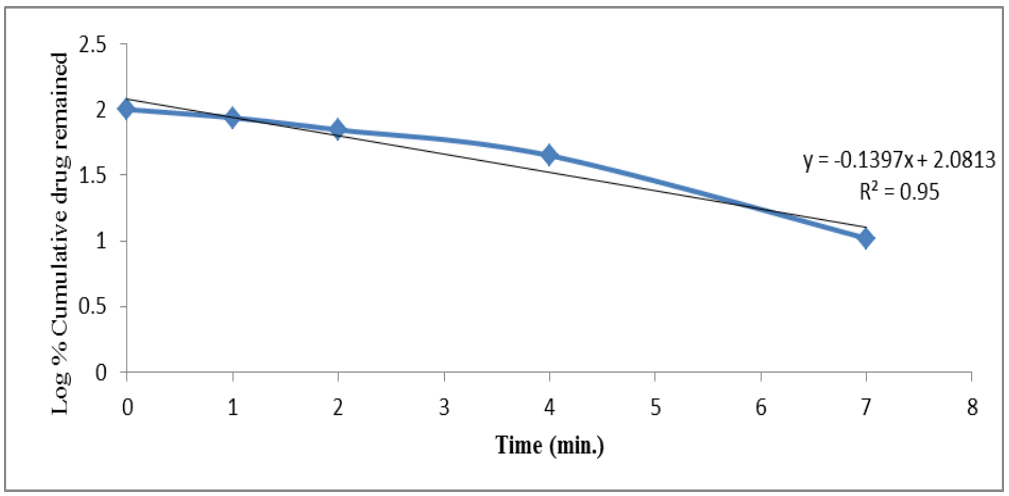

Fig. 22: First order model for formulation F3.

Table 8: Release kinetics of F4.

S. No	Time(hrs)	%Cumulative Drug Release	Square root of time	Log time	Log %cumulative drug release	%cumulative drug remained	Log %cumulative drug remained	Cube root of % Drug Remaining
1	0	0.00	0	0	0	100	2	4.642
2	1	14.08	1	0	1.149	85.91	1.934	4.413
3	2	31.25	1.414	0.301	1.495	68.75	1.837	4.097
4	4	58.59	2.000	0.602	1.768	41.41	1.617	3.460
5	7	94.68	2.646	0.845	1.976	5.32	0.726	1.746

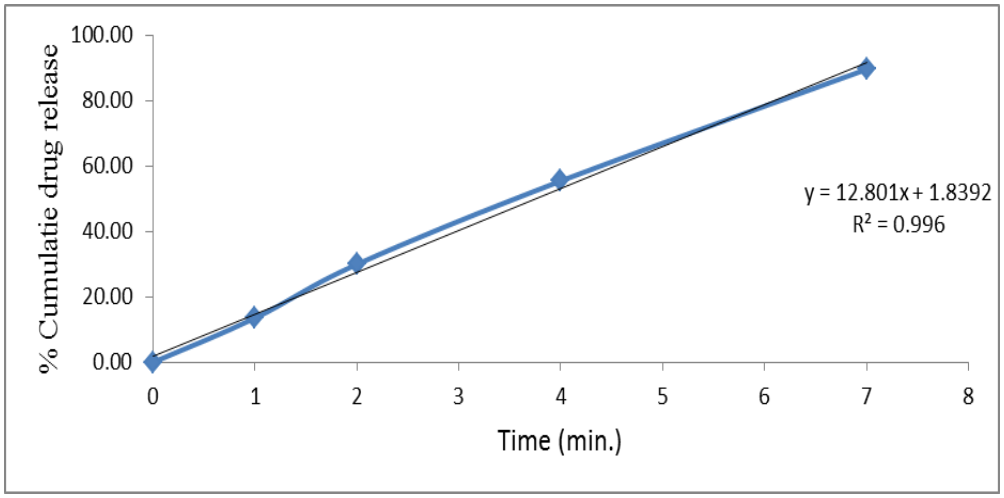

Fig. 23: Zero order model for formulation F4.

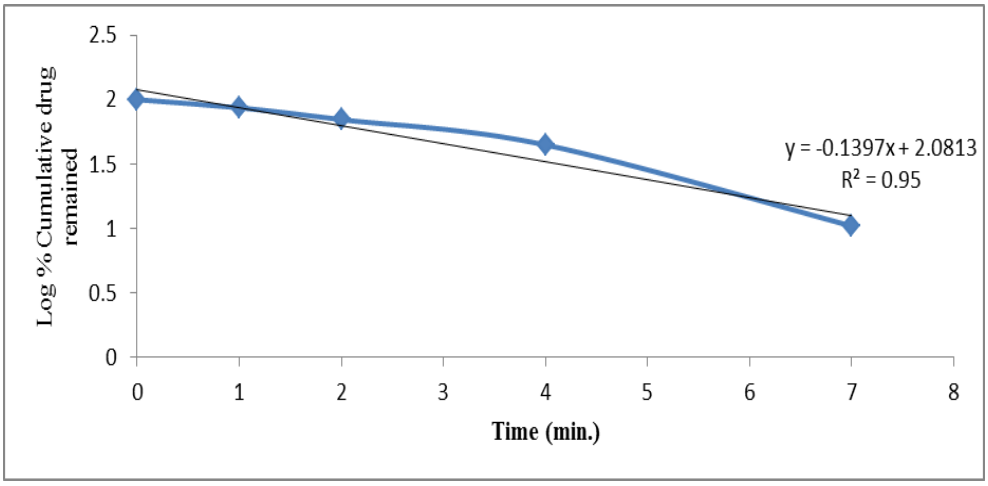

Fig. 24: First Order Model for Formulation F4.

Table 9: Release kinetics of F5.

S. No	Time(hrs)	%Cumulative Drug Release	Square root of time	Log time	Log %cumulative drug release	%cumulative drug remained	Log %cumulative drug remained	Cube root of % Drug Remaining
1	0	0.00	0	0	0	100	2	4.642
2	1	13.41	1	0	1.127	86.59	1.937	4.424
3	2	30.84	1.414	0.301	1.489	69.16	1.840	4.105
4	4	53.79	2.000	0.602	1.731	46.2144	1.665	3.589
5	7	90.04	2.646	0.845	1.954	9.96	0.998	2.152

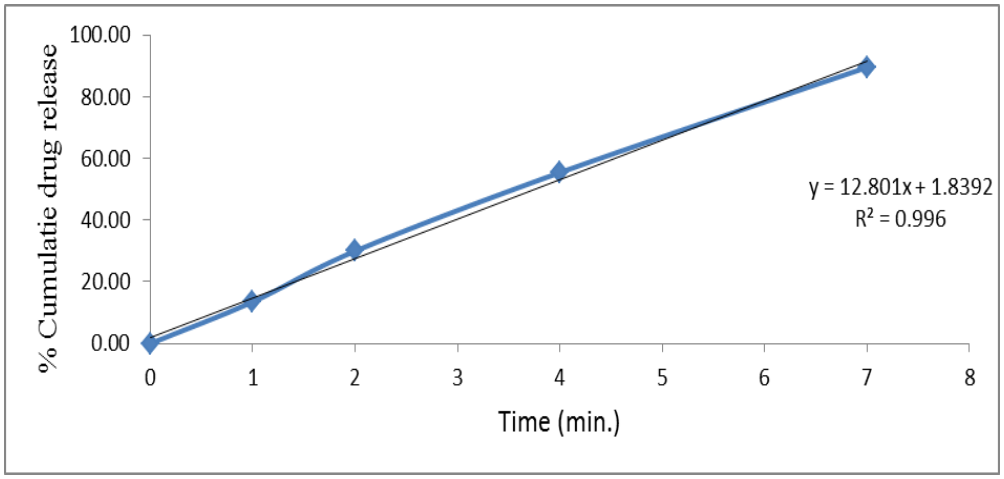

Fig. 25: Zero order model for formulation F5.

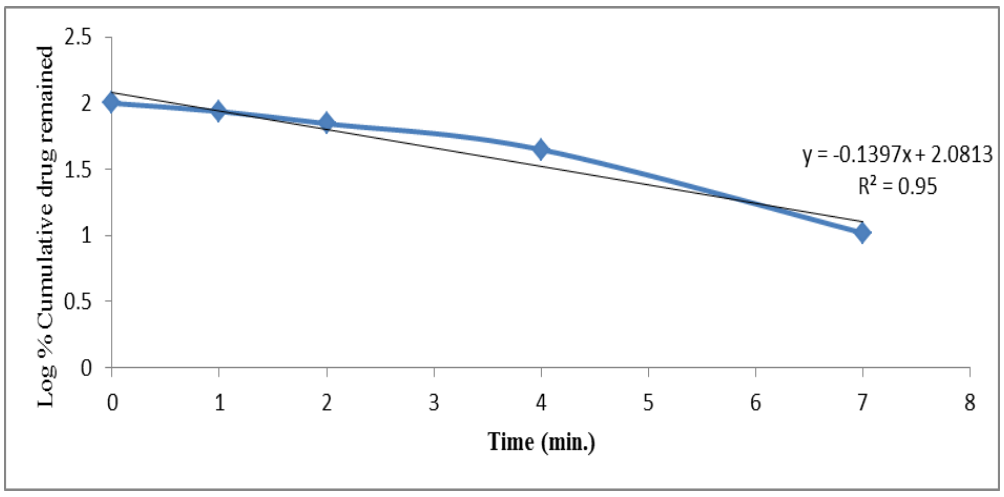

Fig. 26: First order model for formulation F5.

Table 10: Release kinetics of F6.

S. No	Time(hrs)	%Cumulative Drug Release	Square root of time	Log time	Log %cumulative drug release	%cumulative drug remained	Log %cumulative drug remained	Cube root of % Drug Remaining
1	0	0.00	0	0	0	100	2	4.642
2	1	13.41	1	0	1.127	86.59	1.937	4.424
3	2	30.84	1.414	0.301	1.489	69.16	1.840	4.105
4	4	53.79	2.000	0.602	1.731	46.214	1.665	3.589
5	7	90.04	2.646	0.845	1.954	9.96	0.998	2.152

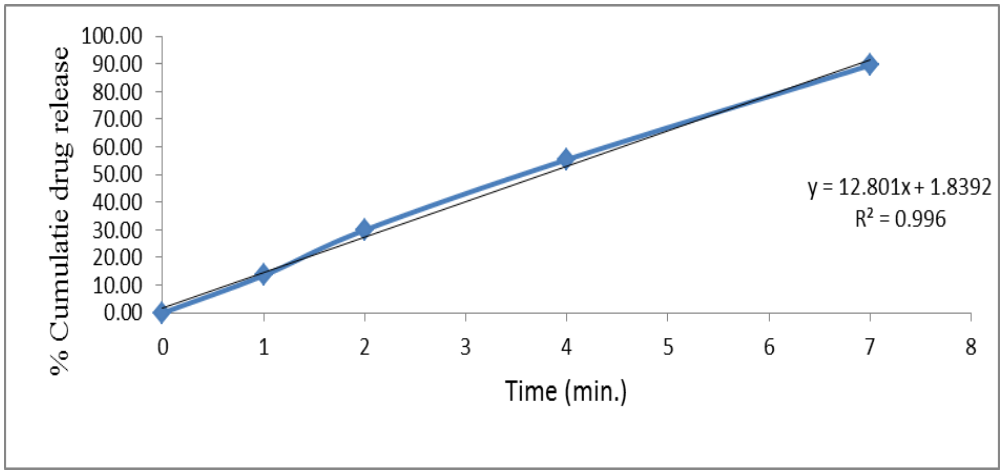

Fig. 27: Zero order model for formulation F6.

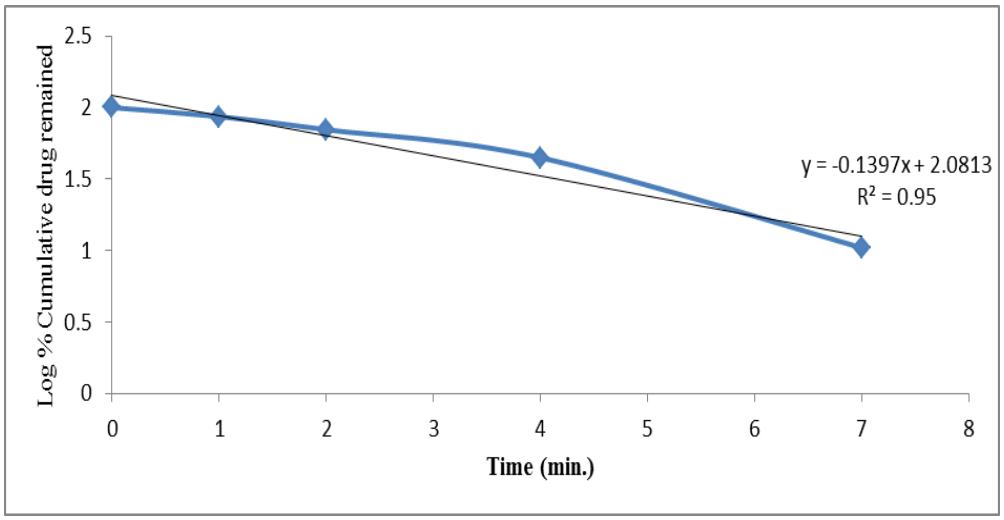

Fig. 28: First order model for formulation F6.

Table 11: Release kinetics of F7.

S. No	Time(hrs)	%Cumulative Drug Release	Square root of time	Log time	Log %cumulative drug release	%cumulative drug remained	Log %cumulative drug remained	Cube root of % Drug Remaining
1	0	0.00	0	0	0	100	2	4.642
2	1	13.14	1	0	1.119	86.86	1.939	4.429
3	2	30.36	1.414	0.301	1.482	69.64	1.843	4.114
4	4	54.24	2.000	0.602	1.734	45.76	1.660	3.577
5	7	88.29	2.646	0.845	1.946	11.71	1.069	2.271

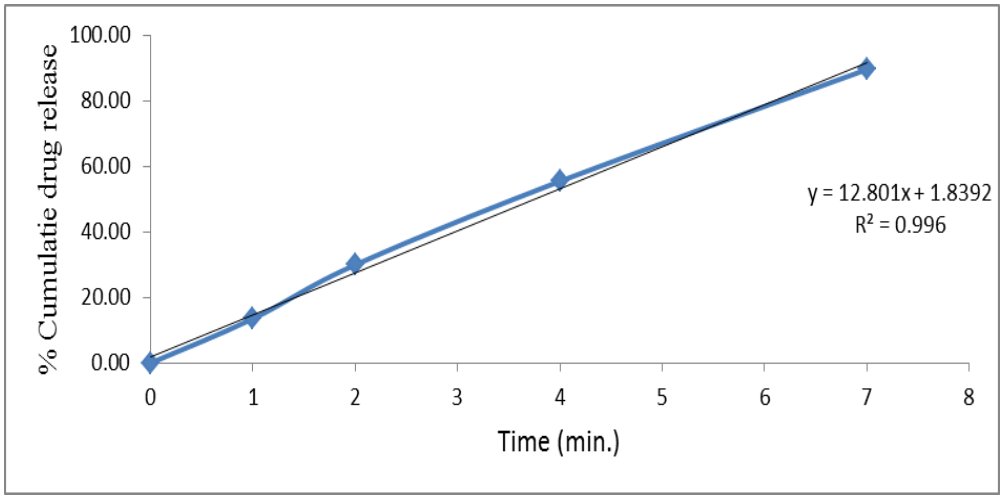

Fig. 29: Zero order model for formulation F7.

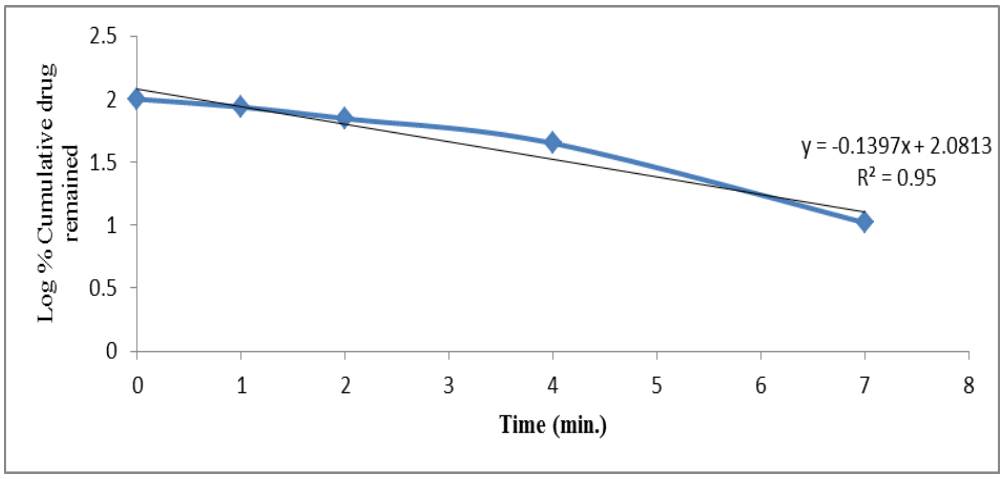

Fig. 30: First order model for formulation F7.

Table 12: Release kinetics of F8.

S. No	Time(hrs)	%Cumulative Drug Release	Square root of time	Log time	Log %cumulative drug release	%cumulative drug remained	Log %cumulative drug remained	Cube root of % Drug Remaining
1	0	0.00	0	0	0	100	2	4.642
2	1	13.52	1	0	1.131	86.48	1.937	4.422
3	2	29.94	1.414	0.301	1.476	70.06	1.845	4.122
4	4	55.41	2.000	0.602	1.744	44.58	1.649	3.546
5	7	89.54	2.646	0.845	1.952	10.46	1.020	2.187

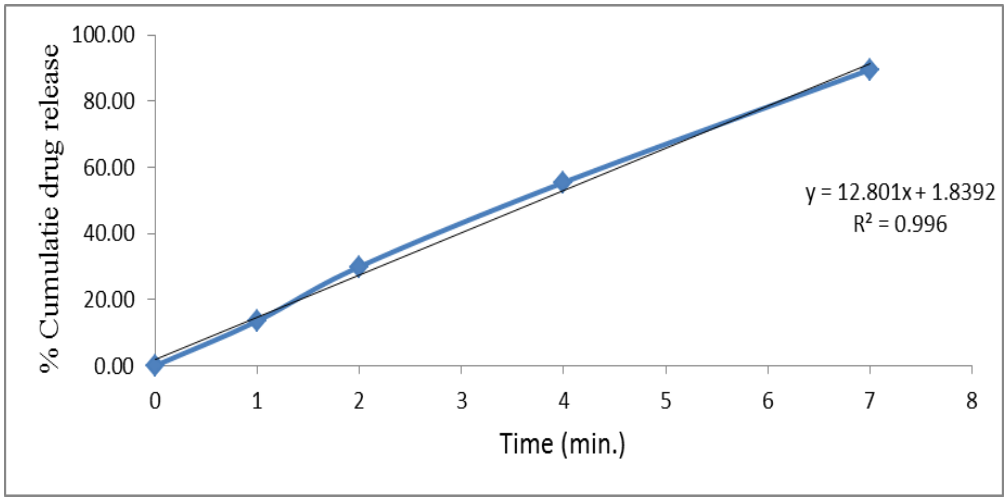

Fig. 31: Zero order model for formulation F8.

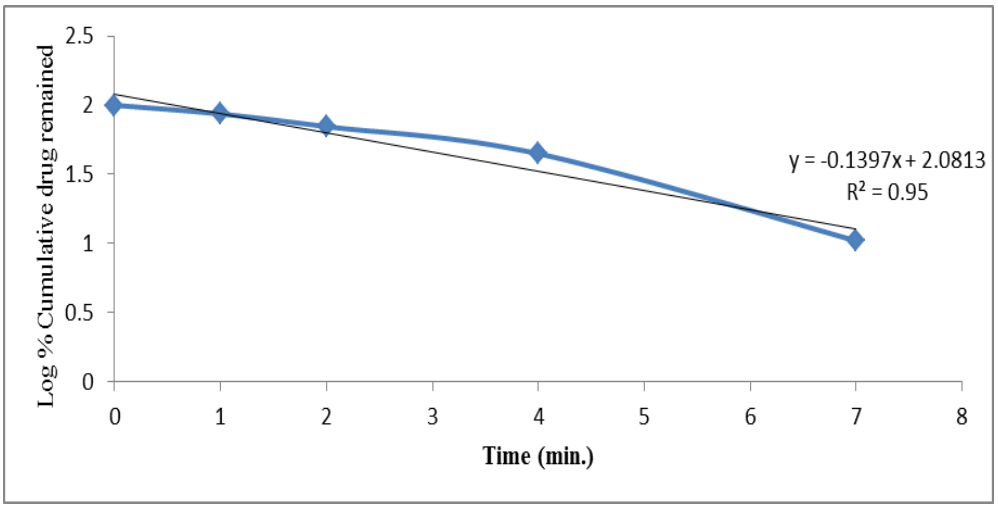

Fig. 32: First order model for formulation F8.

Table 13: Results of kinetic studies timolol formulations.

Formulation	Zero order (R^2)	First order (R^2)	Higuchi's plot (R^2)	Korsemeyer's Peppa's (n)	Hixson Crowell
F1	0.996	0.878	0.939	0.668	0.951
F2	0.998	0.884	0.928	0.681	0.947
F3	0.997	0.918	0.935	0.669	0.964
F4	0.993	0.921	0.938	0.671	0.97
F5	0.995	0.94	0.939	0.671	0.976
F6	0.996	0.951	0.938	0.67	0.982
F7	0.995	0.953	0.941	0.673	0.983
F8	0.994	0.95	0.94	0.672	0.982

All formulations shown the zero order kinetics F1- F8.

4.1 SUMMARY AND CONCLUSION

Eight tablets from each formulation (F1 to F8) were weighed using an electronic balance and the average weight was calculated. The results was found to be F1=148.97±0.03mg, F2=150.01±0.02mg, F3=149.65±0.05mg, F4=148.87±0.08mg, F5=151.57±0.03mg, F6=149.90± 0.02mg, F7=149.51±0.07mg, F8=148.87±0.03mg.

The tablets hardness was decided by using Monsanto hardness tester. It is expressed in kg/cm^2. As we know tablets have resistance to friability and also have a certain amount of strength, to oppose mechanical shocks of handling in the manufacture, packaging, and shipping. 3 tablets were randomly picked from each formulation and values were calculated and found to be F1=3.7±0.28, F2=7.4±0.25Kg/Cm^2, F3=5.7±0.19Kg/Cm^2, F4=6.7±0.23Kg/Cm^2, F5=4.7±0.50 Kg/Cm^2,

F6=3.3±0.23Kg/Cm^2, F7=5.2±0.18Kg/Cm^2, F8=4.7±0.17Kg/Cm^2.

Friability is the measure of tablet strength. Roche type friabilator was mainly used for testing the friability of the tablets. Firstly, we weighed 20 tablets correctly and placed in the fall down apparatus that revolves at 25 rpm dropping the tablets through a distance of six inches with each revolution. After 4 minutes. The tablets were weighed and the percentage loss in tablet weight was found to be F1=0.33±0.08%, F2=0.53±0.05%, F3=0.57±0.09%, F4=0.67±0.05%, F5=0.77± 0.07%, F6=0.37±0.03%, F7=0.47±0.06%, F8=0.50±0.04%.

The thickness of tablets from each formulation was determined in mm using a Vernier caliper (Pico India) and 3 tablets selected from each formulation. The average values were calculated. The results are found to be F1= 2.8±0.32, F2=2.3±0.20, F3=2.6±0.23, F4=2.4±0.18, F5=2.7 ±0.28, F6=2.6±0.11, F7=2.8±0.17, F8=2.5±0.15.

Ten tablets from each formulation were taken for content uniformity test, crushed and mixed. 10 mg of timolol maleate equivalent of the mixture was extracted from the mixture thoroughly with 100 ml of pH 6.8 phosphate buffer. By using UV spectrophotometer at 296 nm, the amount of drug present in each extract was determined. This procedure was continued for three times and the average was taken. The results was found to be F1=98.04±0.035%, F2=99.81±0.015%, F3=99.13±0.032%, F4=96.51±0.028%, F5=94.61±0.039%, F6=98.26±0.029%, F7=97.88±0.032% F8=96.56±0.038%.

In order to investigate the possibility of any side effects In-vivo, first of all, the surface pH of the buccal tablets was determined. As we know that more than 7 or less than 7(alkaline or acidic) pH may cause irritation to the buccal mucosa, so, for this reason, it was determined to keep the surface pH as close to neutral as possible. The surface pH of 8 formulation was found to be F1=6.34±0.038, F2=6.33±0.026, F3=6.22±0.023, F4=6.65±0.025, F5=5.77±0.018, F6=6.17± 0.023, F7=6.01±0.051, F8=5.79±0.035.

In the evaluation of bioadhesion, it is important to use uniform surfaces that allow the formation of reproducible adhesive bonds. In the present study, goat buccal mucosa was used as a model mucosal surface for adhesion testing and the result was found to be F1=36.4±0.02, F2=33.4±0.04, F3=34.1±0.08, F4=31.4±0.03, F5=31.3±0.05, F6=27.5±0.06, F7=29.4±0.04, F8=31.4±0.07gm.

For the calculation of swelling index, first of all, 8 buccal tablets were individually weighed (W1) and placed separately in petri dishes with 5 ml of phosphate buffer of pH 6.8. At the interval of time 1 hr, 2hr, 4 hr, and 8hr, the tablet was removed from the petri dish and excess surface water was removed carefully with filter paper. The swelling index was found to be after 8 hr for formulation F1=82.3%, F2=74.5%, F3=66.1%, F4=71.4%, F5=69.0%, F6=74.3%, F7=71.2%, F8=69.4%.

In-vitro drug release data of formulation F1 to F8 were suitable to zero order, first order equations. The R-value was found to be higher in zero-order followed by first order equation which indicates that all the formulations followed the zero order release pattern. An *in-vitro* dissolution study was designed to carry out in such a way that they mimic *in-vivo* conditions. For *in-vitro* dissolution study, it was confirmed to carry out the dissolution in pH 6.8 phosphate buffer. The formulations F1, F2, F3 & F4 containing drug, carbopol 934p and Polyethylene oxide (PEO) polymers in the ratios of 1:3:9.5, 1:4:8.5, 1:5:7.5 and 1:6:6.5 respectively. The *in-vitro* cumulative drug release profile of formulations F1, F2, F3, and F4 showed 98.36%, 96.90%, 93.36% and 94.64% respectively. Among these four formulations, F1 was found to be highest percentage drug release. During the study, it was observed that the tablets were initially swelled and no erodible over the period of 7 hrs. Similarly the formulations F5, F6, F7 & F8 containing drug, carbopol 934p and sod CMC polymers in the ratios of 1:3:9.5, 1:4:8.5, 1:5:7.5 and 1:6:6.5 respectively. The *in-vitro* drug release profile of formulations F5, F6, F7, and F8 showed 90.10%, 89.15%, 88.25% and 89.5% respectively. Among these four formulations, F5 was found to be highest percentage drug release. During the study, it was observed that the tablets were initially swelled and no erodible over the period of 7 hrs. So here, It was concluded that If formulation containing poly-ethylene oxide polymer was replaced by the formulation containing sodium CMC polymer, then the ratio of formulation F5 showed minimum drug release in comparison to the formulation 1 containing ratio 1:3:9.5. So here, we can say that the formulation F1 *in-vitro* release found to be maximum.

In-vitro drug release data for all the formulations F1 to F8 were subjected to release kinetic study according to zero order kinetics ascertain the mechanism of drug release. So, all the formulations followed zero-order kinetics. The R^2 values of formulation F1 to F8 were found to be F1=0.996, F2=0.998, F3=0.997, F4=0.993, F5=0.995, F6=0.996, F7=0.995, F8=0.994.

5.1 CONCLUSION

Finally, it was observed that timolol maleate mucoadhesive buccal tablets gave acceptable mucoadhesion. Furthermore, since the drug was gradually released from all formulations over a period of 7 hr. The best *in-vitro* drug release profile was achieved with the formulation F1 Such as (98.36%) which contained the drug (timolol maleate), carbopol 934 & Polyethylene oxide polymers in the ratio of 1:3:9.5. It shows that if increasing the concentration of carbopol 934, the drug release rate was found to be decreased. But

when the concentration of Polyethylene oxide increased then the drug release rate was found to be increased. The *in-vitro* release kinetics studies exhibit that all formulation suitable for the zero order kinetics. Moreover, a complex *in-vivo* study is to be carried out for the best formulation using a suitable animal model.

6.1 ACKNOWLEDGEMENT

The author thanks to Dr. Vandana Arora Sethi and Mr. Vivek Dhiyani for his valuable suggestion during this research project work.

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