Research Article

Available Online at: www.ijpir.com

International Journal of Pharmacy and Industrial Research

ISSN Print 2231 – 3648
Online 2231 – 3656

Design and evaluation of sublingual atenolol tablets

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ABSTRACT

The research objective of this study is to formulate and evaluate sublingual Atenolol tablets. The drug Atenolol is a selective β_1 receptor antagonist, a drug belonging to the group of beta blockers which is a class of drugs used primarily in Hypertension. The compatibilities studies were performed by using the FTIR spectroscopy. The pre-formulation studies such as Bulk Density, Tapped density hausner's ratio were performed. Here we have used the direct compression technique to prepare optimized tablet formulation, containing Atenolol, Mannitol, sodium starch glycolate, talc provides a short DT of 60 sec with sufficient crushing strength and satisfactory friability, containing oral tablet. The Chitosan and Piperine were used in different concentration in formulation and the different Post compression parameter evaluation was performed and *in vitro* dissolution study was done by using the dissolution apparatus. The permeation study was carried on modified Franz diffusion cell. This study shows as all the post and pre formulation parameters were in the range as standard and the concentration of super disintegrate has significant effect on disintegration time.

Keywords: Atenolol, Bioavailability, Permeability enhancement, Hypertension.

INTRODUCTION

Oral Drug Delivery

The Oral mucosal drug delivery is an alternative and effective method of systemic drug delivery that offers several advantages over both injectable and enteral methods. Because the oral mucosa is highly vascularised, drugs that are absorbed through the oral mucosa directly enter the systemic circulation, bypassing the gastrointestinal tract and first-pass metabolism in the liver. For some drugs, this results in rapid onset of action via a more comfortable and convenient delivery route than the intravenous route. Not all drugs, however, can be administered through the oral mucosa because of the characteristics of the oral mucosa and the physicochemical properties of the drug. (Zhang *et al*., 2002)

MATERIALS AND METHODS

The following materials were used for the development of formulation

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S. No.	Material	Supplier
1.	Atenolol	Cipla Ltd. Mumbai
2.	Cellulose microcrystalline	Central Drug House, New Delhi
3.	Cross Carmi lose sodium	Central Drug House, New Delhi
4.	Piperine	Sanat Product ltd
5.	Chitosan	Central Drug House, New Delhi
6.	Talc	Central Drug House, New Delhi
7.	Magnesium stearate	Central Drug House, New Delhi

Preparation of Standard Curve of Atenolol

Exactly 100 mg of atenolol was taken in a 100ml volumetric flask and Phosphate buffer pH–6.8 was added into it. Then volume was made up to the mark by same solution. Different volumes of aliquots of the solution were taken in 10 ml volumetric flask and the volume was made up to the mark. Thus different concentrations of atenolol ranging from 10.0 to100.0 µg/ml were obtained. Then the absorbance of the solutions was recorded at 274.3 nm. The absorbance vs. concentration curve was plotted.

Formulation of Tablets (Sudarshan *et al*., 2012; Gottumukkula., *et al* 2014; arti *et al*., 2014)

Direct Compression is the process by which tablets are compressed directly containing mixtures of the drug and excipients without any preliminary treatment. In this process, directly compressible diluents like mannitol, Microcrystalline cellulose, Chitosan, Piperine, Magnesium Streate and Talc are mixed with the drug and other excipients to produce a uniform mixture and compressed into tablet 1.

Table 1: Composition of Formulations

Ingredients	Formulations								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Atenolol	25	25	25	25	25	25	25	25	25
MCC	28	28	28	28	28	28	28	28	28
Mannitol	57.0	56.5	56.0	55.5	57.0	56.5	56.0	55.5	58.0
Chitosan	1.0	1.5	2.0	2.5	-----	--------	-------	-----	-------
Piperine	-------	-------	------	------	1.0	1.5	2.0	2.5	------
CCS	08	08	08	08	08	08	08	08	08
Mg. Stearete	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Talc	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75

Melting Point

Melting point of atenolol was found to be in the range 153^0C, which complied with Indian Pharmacopoeia standards, indicating purity of the drug sample.

UV Scan of the drug in Phosphate Buffer pH-6.8

From the above scanning report the λmax was found to be 274.3 nm. The absorbance values and λmax are shown in Fig 1. The scanning range was in between 200 nm to 800 nm.

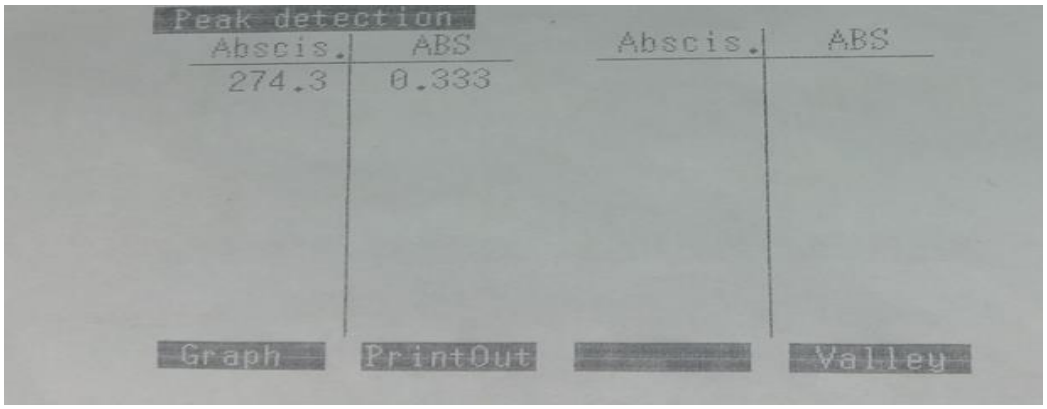


Fig 1: UV Scan of Pure Atenolol

Preparation of Standard Curve of Atenolol in Phosphate buffer pH – 6.8

Graph of absorbance Vs concentration was plotted (λ max 274.3 nm) and found to be linear over the range of 10 to 50 µg/ml obtained indicating its compliance with beer's and lamberts' law. The solution concentration and absorbance for a standard plot.

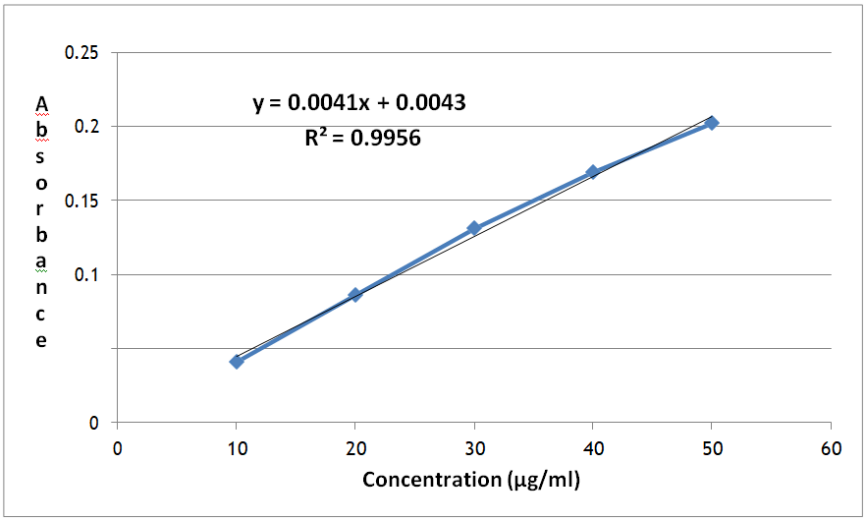


Fig 2: Standard Calibration Curve of Atenolol in Phosphate Buffer pH – 6.8

Fourier Transform Infra-red Spectroscopy Studies

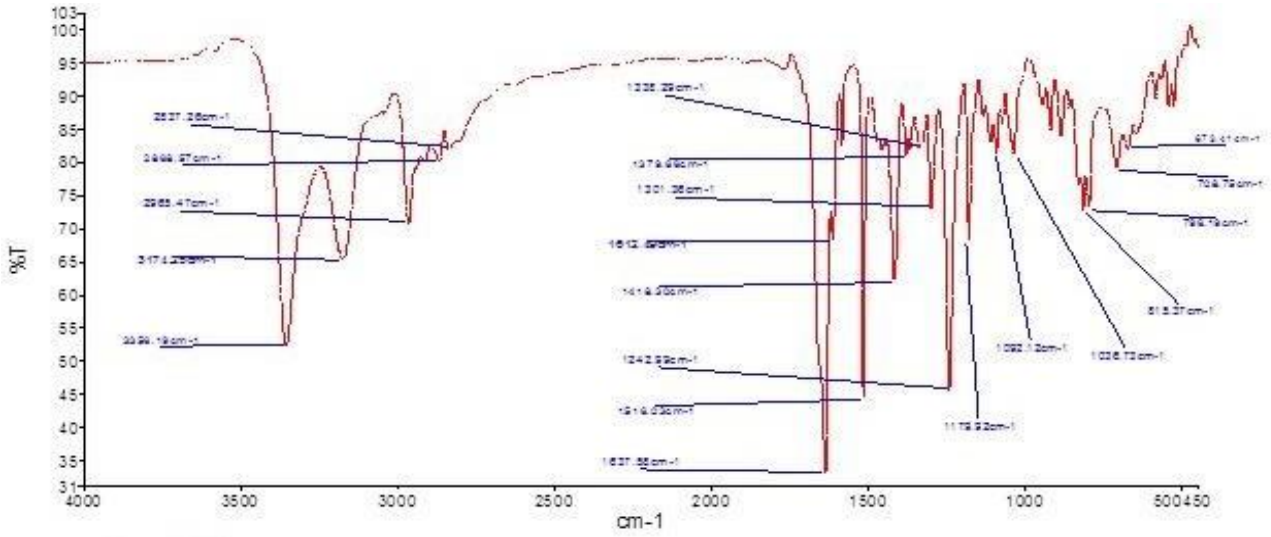


Fig 3: IR Spectra of Atenolol

Pre-Compression Parameter

The powder mixtures of all the formulations were tested by various studies including angle of repose, bulk density, tapped density, Hausner's ratio and Carr's index. All the results showed moderate flow property.

Table 2: Preformulation Study of Powder Mixtures

Formulation	BD (mg/ml)	TD (mg/ml)	Carr's index	Hausner's ratio	Angle of repose (ɵ)
F1	0.36±0.0076	0.42±0.005	12.76±2.86	1.14±0.038	33.98±0.75

F2	0.35±0.00	0.41±0.004	13.69±1.031	1.15±0.013	34.85±0.89
F3	0.35±0.00	0.41±0.009	13.09±2.62	1.15±0.026	34.86±0.22
F4	0.36±0.007	0.41±0.009	12.03±1.95	1.13±0.025	34.40±0.19
F5	0.36±0.007	0.41±0.009	12.03±1.95	1.13±0.025	34.85±0.44
F6	0.36±0.014	0.41±0.009	11.91±2.86	1.13±0.065	34.89±0.25
F7	0.36±0.007	0.42±0.017	13.22±2.32	1.15±0.054	35.07±0.14
F8	0.36±0.007	0.42±0.000	12.16±1.83	1.13±0.024	34.84±0.22
F9	0.36±0.007	0.41±0.18	9.70±3.13	1.11±0.064	34.96±0.08

The values are mean value of 3 observations (N=3) and values in parenthesis are standard deviation (±SD)

Post Compression Parameter for Formulations (F1 – F9)

The physicochemical characterizations are discussed below. The thickness and diameter of formulations from F1 to F9 were measured by digital thickness tester, hardness of formulations from F1 to F9 was measured by Monsanto tester, friability of all the formulations was measured by Roche friabilator and weight variation of different formulations (F1 to F9) were done and showed satisfactory results as per Indian pharmacopoeia (IP) limit.

Table 3: Post Compression Parameter

Formulation	Thickness (mm)	Diameter (mm)	Wt. variation (mg)	Hardness (kg/cm^2)	Friability (%)
F1	6.20±0.04	3.61±0.02	121.8±0.63	3.47±0.15	0.65±0.12
F2	6.21±0.04	3.62±0.02	120.9±0.85	3.3±0.30	0.56±0.04
F3	6.20±0.05	3.61±0.01	119.4±1.36	3.03±0.20	0.73±0.02
F4	6.21±0.03	3.61±0.03	122.3±0.95	3.17±0.15	0.76±0.08
F5	6.20±0.04	3.60±0.01	121.5±1.69	3.23±0.25	0.69±0.12
F6	6.21±0.05	3.61±0.02	120.7±0.99	3.5±0.10	0.73±0.11
F7	6.21±0.05	3.60±0.02	118.8±1.02	3.5±0.10	0.85±0.13
F8	6.20±0.04	3.61±0.03	119.5±1.23	3.2±0.10	0.64±0.11
F9	6.20±0.04	3.61±0.02	122.0±0.96	3.53±0.15	0.72±0.008

Disintigration Time Wetting Time And Assay Of Different Formulation (F1-F9)

Table 4: Disintegration Time Wetting Time and Assay of Different Formulation

Formulation	Disintegration time (sec)	Wetting time(sec)	Assay(%)
F1	64.66±0.57	54.33±3.51	98.85±1.51
F2	58.00±1.00	48.00±1.00	96.72±1.37
F3	59.66±2.08	49.66±2.08	96.61±1.52
F4	61.33±2.08	51.33±2.08	98.46±0.73
F5	56.33±1.52	47.66±1.52	98.99±1.25
F6	59.33±1.52	49.00±2.64	97.73±1.41
F7	58.00±1.00	46.00±1.73	97.12±1.59
F8	56.33±1.52	46.00±2.64	98.06±0.78
F9	60.33±2.08	51.00±2.64	96.46±0.1.1

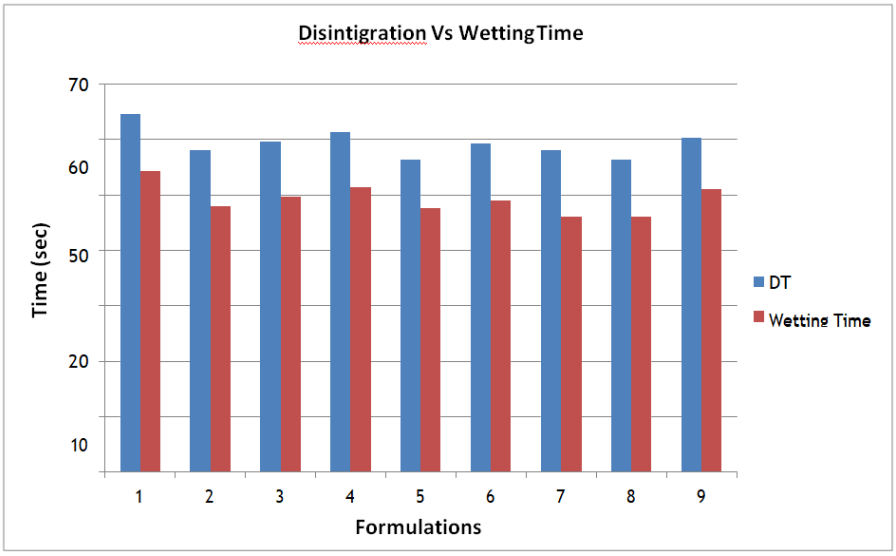


Fig 4: Bar Graph between Disintegration time Vs Wetting time

IN VITRO DRUG RELEASE PROFILE

The sublingual tablets were subjected for dissolution study by using modified USP dissolution apparatus. The tablet was placed in the basket and the dissolution was carried out using Phosphate Buffer pH 6.8 as medium. Aliquots of 5ml were withdrawn at every 5 minutes interval and were replaced by same solution. The drug content was analyzed spectrophotometrically at 274.3 nm against reagent blank and calculate the percentage drug release.

Table 5: *In Vitro* Drug Release Profile

Time (Min.)	Formulation								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
5	18.69±1.67	20.16±1.67	22.35±0.63	23.08±00.63	26.37±0.63	26.74±0.63	24.18±0.36	25.28±0.63	25.64±0.63
10	34.79±1.09	34.06±0.63	36.25±0.63	38.45±0.0.63	39.54±0.63	39.91±0.63	42.84±0.36	39.91±0.63	38.45±0.63
15	44.30±1.67	45.40±1.26	46.25±0.63	47.59±1.67	53.81±1.67	53.08±0.63	58.20±0.36	54.18±0.63	48.69±0.63
20	57.10±0.63	58.20±1.26	59.30±0.63	60.76±0.63	66.25±1.67	70.28±0.63	69.54±0.36	68.08±0.63	56.01±0.63
25	70.28±0.63	73.93±0.63	74.30±1.09	75.76±0.63	78.69±1.09	76.13±1.36	78.32±0.36	78.32±1.67	62.23±1.09
30	73.93±0.63	77.23±0.63	83.08±1.09	84.18±1.09	87.10±1.67	86.74±0.63	88.93±0.36	90.76±1.67	84.08±1.09

The values are mean value of 3 observations (N=3) and values in parenthesis are standard deviation (±SD)

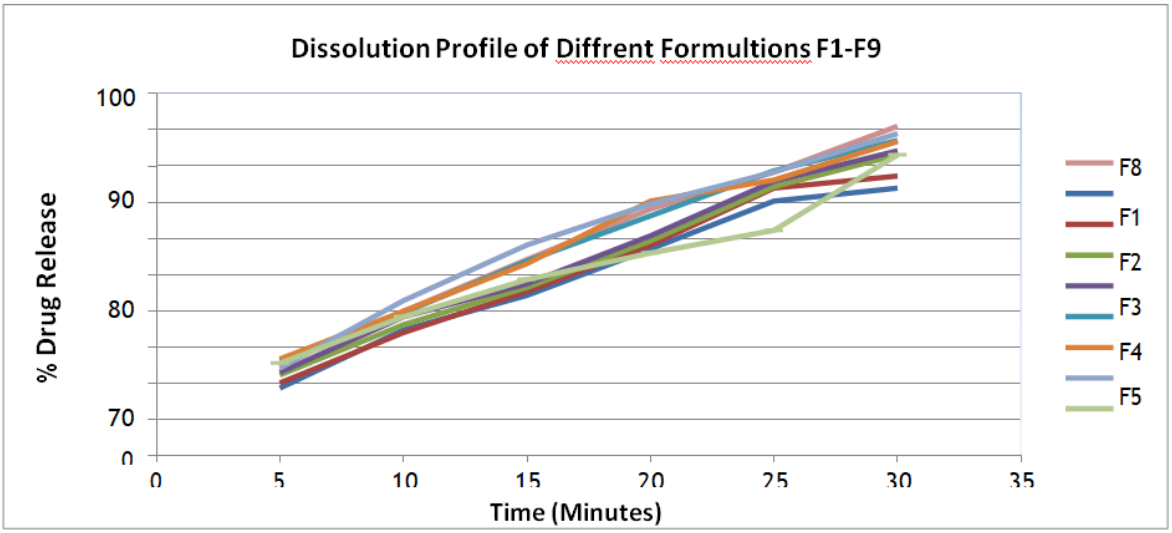


Fig 5: Dissolution Profile of Different Formulations (F1-F9)

The dissolution study was carried out using 900ml of pH 6.8 phosphate buffer dissolution medium at 50 rpm at 37^0C± 0.5^0C. Formulations 7 and 8, showed rapid dissolution rate, the percentage cumulative drug release (%CDR) after 30 minutes found in Formulation 8 is 90.76. Thus it may be concluded that formulation 7 and 8 may be considered as best formulation with respect to *in vitro* drug release profile.

PERMEABILITY STUDY

The Permeability study of tablet was done using the Franz diffusion cell,which shows increase permeability of tablet. The dissolution was carried out using Phosphate buffer pH 6.8 as medium. Aliquots of 5ml were withdrawn at every 5 minutes interval and were replaced by same solution. The drug content was analyzed spectrophotometricallyat 274.3 nm against reagent blank and percentage drug release was calculated.

Table 6: Drug Release from Diffusion Cell

Time	Formulation								
(Min.)	F1	F2	F3	F4	F5	F6	F7	F8	F9
05	15.49±0.25	15.97±0.07	16.83±0.30	16.10±0.28	13.94±0.18	17.80±0.37	18.82±0.30	20.28±0.18	10.73±0.25
10	16.67±0.12	17.15±0.12	18.74±0.32	18.5±0.32	18.70±0.28	20.57±0.43	25.69±0.24	26.46±0.30	13.05±0.18
15	22.72±0.25	24.67±0.42	24.92±0.18	24.15±0.37	30.16±0.14	35.53±1.03	41.5±0..18	44.1±0.53	18.45±0.42
20	36.10±0.18	38.33±0.07	41.3±0.24	44.19±0.39	40.28±0.39	47.11±0.61	51.18±0.32	54.84±0.24	23.13±0.53
25	47.36±0.37	49.84±0.24	51.34±0.49	52.44±0.50	53.5±0.0.32	59.59±0.24	67.97±0.25	73.70±0.60	34.47±0.12
30	51.63±0.71	58.62±.0.55	59.31±0.57	61.38±0.30	68.21±0..18	71.71±0.49	80.49±0.50	89.46±0.30	47.32±0.18

The values are mean value of 3 observations (N=3) and values in parenthesis are standard deviation (±SD)

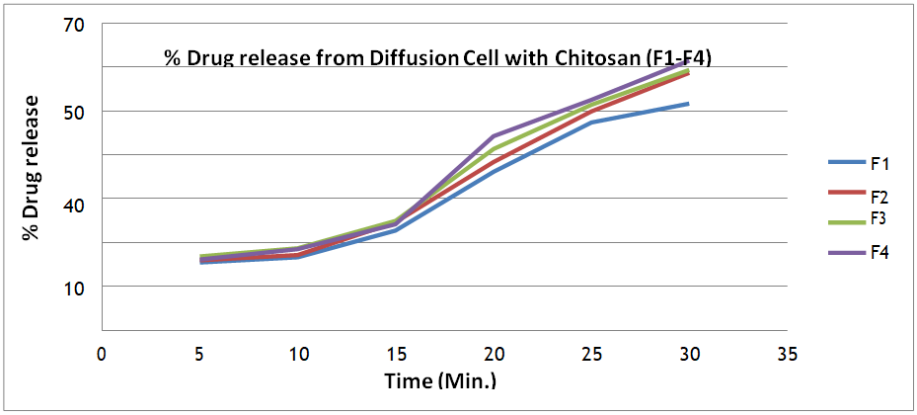


Fig 6: Percentage Drug release from Diffusion Cell with Chitosan (F1-F4)

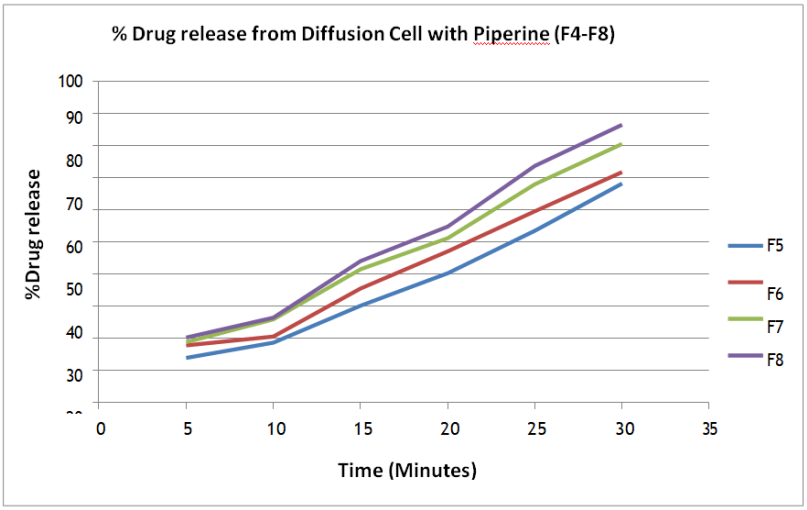
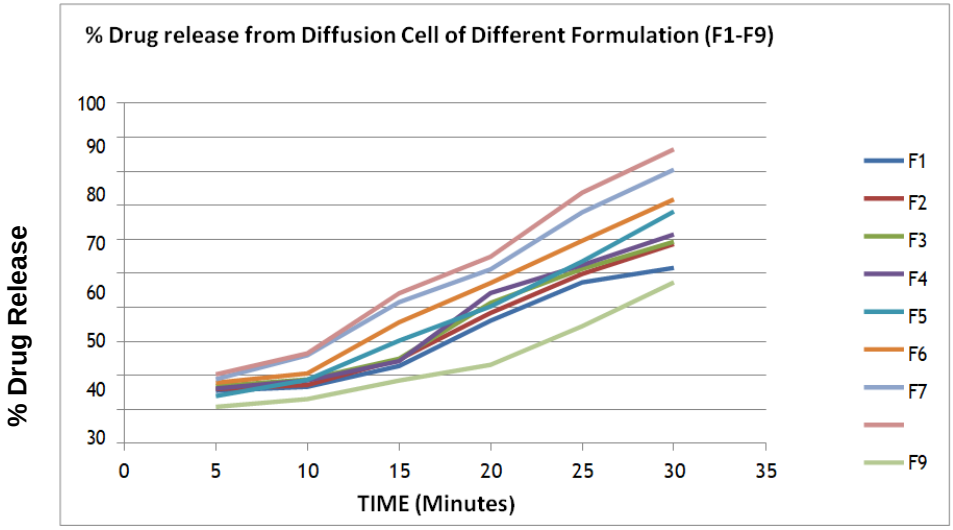


Fig 7: 5.12 Percentage Drug release from Diffusion Cell with Piperine



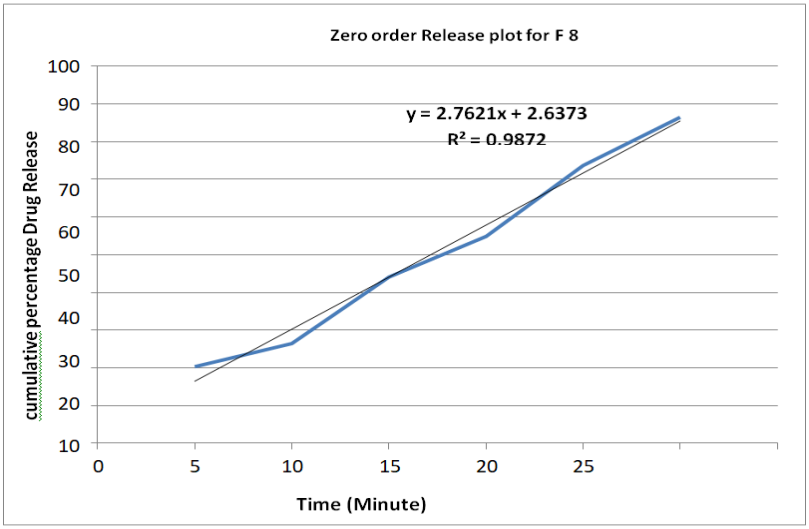
The Permeability study was carried out using 100ml of pH 6.8 phosphate buffer in Franz Diffusion call at $37^0C \pm 0.5^0C$.

Fig 8: Percentage Drug release from Diffusion Cell of Different Formulation (F1-F9)

Formulations 4 and formulation 8, showed rapid drug release through Membrane, the percentage cumulative drug release (%CDR) after 30 minutes found in Formulation 8 is 89.46. Thus it may be concluded that formulation 4 considered as best formulation with respect to *Ex vitro* drug release profile with Chitosan and Formulation 8 may be considered as best formulation with respect to *Ex vitro* drug release profile with piperine.

Zero Order Kinetics

In the Zero order, the graph was plotted between time and cumulative % drug release for the determination of regression coefficient.



zero order release profile for Formulation 8 was plotted and regression coefficient 0.9872 was obtained.

Fig 9: Zero Order Release Plot for F 8

First Order Kinetics

In the First order, the graph was plotted between time and log remaining % drug release for the determination of regression coefficient.

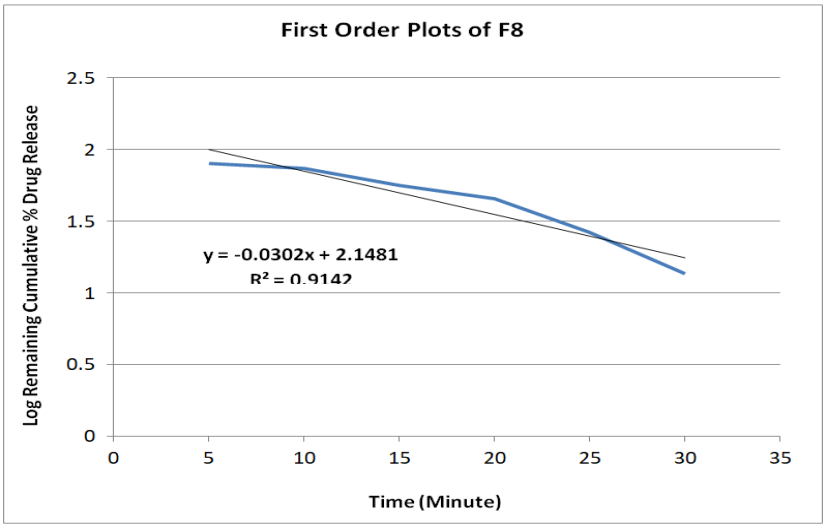


Fig 10: First Order Plot of F8

First order release profile for Formulation 8 was plotted and regression coefficient 0.9142 was obtained.

SUMMARY AND CONCLUSION

The Atenolol is a beta-adrenoreceptor antagonist (beta-blocker) used in the treatment of hypertension and angina pectoris. It is incompletely absorbed from the gastrointestinal tract and has an oral bioavailability of only 40%. This is because of poor absorption in lower gastrointestinal tract. Therefore, it was selected for the design of a sublingual drug delivery with a view to improve its oral bioavailability and permeability. In the present study, an attempt was made to design and optimize sublingual drug delivery system of atenolol using Piperine and Chitosan to increase the Permeability. The compatibility evaluations were performed by Fourier transforms infra-red spectroscopy, Studies implied that polymers and drug were compatible with each other. There was no interaction found between polymer and drug. Estimation of atenolol in the prepared formulations was carried out by extracting the drug with Phosphate Buffer pH 6.8 solutions and the absorbance was measured at 274.3 nm. The powder mixtures of all the formulations were tested by various studies including angle of repose, bulk density, tapped density, Hausner's ratio and Carr's index. All the results showed moderate flow property. The data was presented in Table No. 5.4. The tablets were prepared by direct compression method, In the formulation the composition of excipients Mannitol as diluents, MCC as Binder, Chitosan and Piperine used as Permeation enhancer and Talc as Glident. Totally nine batches of preliminary trial formulations were designed and from the results of evaluation data, all the formulations were evaluated for hardness, friability, drug uniformity, weight variation, wetting time and disintegration time. It was observed that all the tablets of all batches had acceptable physical characteristics. *In vitro* drug release study was performed using USP dissolution test apparatus-II at 50 rpm using 900 ml of Phosphate buffer pH 6.8 maintained at 37±0.5ºC as the dissolution medium. The study was carried out for 30 Minutes and found the Formulation 7 and Formulation 8 Shows the maximum percentage drug release. The permeability study was performed using Franz diffusion cell using 100 ml of Phosphate Buffer maintained at 37 ± 0.5ºC. The Study carried out for 30 Minutes and it showed that the 4 Formulation with Chitosan and 4 Formulation With Piperine its shows that formulation With Chitosan shows 61.34 % Drug Release and Formulation with piperine maximum drug release 89.46% . Its Shows that piperine is best permeability enhancer with atenolol. The data shown in table. From the present study it is concluded that it offers a valuable sublingual dosage form. The sublingual tablets of atenolol provide a better option for increasing the bioavailability and reliability for treatment of hypertension. This dosage form is associated with many advantages like quick onset of action and it by passes the liver. The permeability studies shows its increase the permeability of drug with piperine. The kinetic release study shows the formulation follows zero order kinetics with highest R^2 value.

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