wjpmr, 2021,7(10), 198-208

SJIF Impact Factor: 5.922

WORLD JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.wjpmr.com

Research Article

ISSN 2455-3301

WJPMR

FORMULATION AND EVALUATION OF DOXAZOSIN MESYLATEFAST DISSOLVING ORAL STRIPS

Mahaveeraswamy B. M., Bhagawathi S. T.* and Manjunath K.

Sree Siddaganga College of Pharmacy, B.H. Road.

***Corresponding Author: Bhagawathi S. T.**

Sree Siddaganga College of Pharmacy, B.H. Road.

Article Received on 16/07/2021 **Article Revised on 06/08/2021** **Article Accepted on 26/08/2021**

ABSTRACT

An objective of the hypertension treatment is to suppress the blood pressure in a faster onset of action. This is generally achieved by drug to be administers directly into the blood circulation through the Buccal mucosa by using fast dissolving strips formulation. The drug to be administered in the Buccal route through GIT it can be metabolized more for this reason drug can be administered in the Buccal mucosa by using strips formulation give fast onset of action. The objective of this research work was to improve the bioavailability of the drug and fast the onset of action to decrease the blood pressure. The Buccal bioavailability of Doxazosin mesylate is only 60% for this reason drug can be administrated into Buccal mucosa using mucoadhesive strips. Fast dissolving Buccal strips were prepared by solvent casting method using various polymers like hydroxyl propyl methyl cellulose E15, PVP K-30, PVA and Glycerol as plasticizer and saccharin as a sweetening agent and vanillin as a flavoring agent. Dissolution profile as studied in a USP dissolution apparatus type 1 using a pH 6.8 simulated saliva. The influence of variable like polymer type, concentration, of Doxazosin mesylate release profile was studied. The formulation was optimized on the basis of various evaluation parameters like drug content and in vitro drug release. Formulation F6 successfully fast the release of drug within 8 minutes.

KEYWORDS: Doxazosin mesylate, HPMC E 15, PVP K-30, PVA, Vanillin.

INTRODUCTION

Blood pressure is the force of blood against the artery walls as it circulates through the body. High blood pressure or hypertension is the constant pumping of blood through blood vessels with excessive force.[1]

Blood pressure is written as two numbers. The first (systolic) number represents the pressure in blood vessels when the heart beats. The second (diastolic) number represents the pressure in the vessels when the heart rests between beats.

Blood pressure is measured in millimeters of mercury (mmHg). We have hypertension when our pressure is greater than either 140 mmHg systolic pressure or 90 mmHg diastolic pressure, which are the standard uppermost limits of normal. Blood pressure is considered very high when it is more than 180 mmHg systolic or 110 mmHg diastolic the greater the pressure.[2-3]

Fast dissolving strips[4-5]

However, the fear of taking solid tablets and the risk of choking for certain patient population still exist despite their short dissolution/disintegration time. Recent development in novel drug delivery system aims to enhance safety and efficacy of drug molecules by formulating a convenient dosage form for administration. One such approach is rapidly dissolving strips. It consists of a very thin oral strip, which releases the active ingredient immediately after uptake into the oral cavity. Rapid strips combines all the advantages of tablets (precise dosage, easy application)

Advantages of fast dissolving strips[6-7]

- Improved oral bioavailability of drug as hepatic first pass effect is reduced.
- Fast onset of action as drug enters directly in the systemic circulation.
- No fear of obstruction or chocking.
- No need of water during strips administration.
- Reduction in dose of the drug.
- Taste masking
- Improved patient compliance.
- Enhanced stability
- Large surface area strips lead to quick disintegration and dissolution within oral cavity.
- Available in various sizes and shapes

Disadvantages of fast dissolving strips[8]

- Drugs whose therapeutic dose is greater than 40mg cannot be incorporated in the strips.
- Packaging of strips is difficult and it requires special

equipment's.

- Challenge of maintaining dose uniformity in strips.
- Technical limitation of maintaining uniform thickness of strips while manufacturing on large scale.

Criteria for selecting a suitable drug candidate

- Drug should have pleasant taste.
- Therapeutic dose of the drug should not be greater than 40mg
- Drug should have good solubility in water and saliva.
- It should be stable in water.
- Drug should be partially unionized at oral cavity PH.
- Drug should have small molecular size and low molecular weight.
- Drug molecule should have the capability to permeate oral mucosa

Method of preparation of fast dissolving oral strips[9]

Solvent casting method

The strips are preferably formulated using the solvent casting method. The required quantity of polymer was added in small quantities and mixed well to dissolve in distilled water. Small quantity of drug is dissolved in the above solution. Add plasticizers to the above solution and mixed well. Solution was then casted on Petri dish and kept in hot air oven for drying at 40° C. After drying strips were removed with the help of sharp blade and kept in desiccator for 24 hrs. Then cut into pieces of the desired shape and size.[10]

MATERIALS

Doxazosin mesylate Hydroxypropyl methyl cellulose (HPMC E15), Polyvinyl alcohol (PVP), Polyvinyl pyrrolidone (PVP), from Yarrow chemicals. All other chemicals used were of analytical grade.

Standard Curve of Doxazosin mesylate

Doxazosin mesylate is a white fine powder which was soluble in Simulated saliva pH 6.8. Though several methods are reported for its estimation, the UV spectrophotometric method was employed in the study. Doxazosin mesylate shows maximum absorbance at 246 nm in simulated saliva pH 6.8. Based on this information, a Standard graph was constructed (Figure No.1)

Drug-polymer interaction study of strips

There is always a possibility of drug-excipients interaction in any formulation due to their intimate contact. The technique employed in this study to know drug- excipients interactions is IR spectroscopy. IR spectroscopy is one of the most powerful analytical techniques which offer the possibility of chemical identification. Infra-red spectra of pure drug Doxazosin mesylate and formulations were scanned by using FTIR, by a thin strips method.

Formulation of fast dissolving oral strips

From the preliminary physical observation of the strips prepared the best compositions were used for the incorporation of Doxazosin mesylate solvent casting. Doxazosin mesylate 12mg is dissolved in 2ml ethanol, then polymers are added (PVA, PVP K30, HPMC E15), propylene glycol (plasticizer) was added and stirred to form a homogeneous solution. Finally Vanillin and Sodium saccharin are added and stirred to form a homogeneous mixture. The solution was casted in a mould 6×8 cm (length and width). Then kept in hot air oven at 60ºC for 24 hours. The film thus formed was cut into size of 2×2 cm square strips. The prepared square thin orals strips were packed using single pouches, blister card with multiple units, multiple-unit dispenser, and continues roll dispenser aluminum pouch and stored in desiccator.[11]

Table 1: Composition of different formulation of Doxazocin mesylate fast dissolving oralstrips.

Formulation	Polymer and its composition(mg)				Plasticizer (mL) glycol	Ethanol	Sodium saccharin (mg)	Vanillin (mg)	D.water (mL)
	DM	HPMC E15	PVP K30	PVA					
F1	12mg	300			0.1	2ml	2	2	10
F2	12mg	400			0.1	2ml	2	2	10
F3	12mg	500			0.1	2ml	2	2	10
F4	12mg	200	100		0.1	2ml	2	2	10
F5	12mg	200	200		0.1	2ml	2	2	10
F6	12mg	300	200		0.1	2ml	2	2	10
F7	12mg	200		100	0.1	2ml	2	2	10
F8	12mg	200		200	0.1	2ml	2	2	10
F9	12mg	300		200	0.1	2ml	2	2	10

Evaluation of Doxazosin mesylate buccal strips

a) Physical appearance and surface texture of strips

This parameter was analysed simply with visual inspection of strips and evaluation of texture by feel or touch.

b) Weight uniformity of strips

3 strips of the size 2×2 cm was weighed individually using digital balance and the average weights were calculated.

c) Thickness of strips

Thickness of the strips was measured using screw gauge with a least count of 0.01mm at different spots of the strips. The thickness was measured at three different spots of the strips and average was taken.

d) Folding endurance of patches

The flexibility of strips can be measured quantitatively in terms of what is known as folding endurance. Folding endurance of the strips was determined by repeatedly folding a small strip of the strips (approximately 2x2 cm) at the same place till it broke. The number of times strips could be folded at the same place, without breaking gives the value of folding endurance.

e) Drug content uniformity of strips

The strips were tested for drug content uniformity by UV Spectrophotometric method. strips of 2×2 cm size were cut from three different places from the casted strips. Each strips was placed in 100 mL volumetric flask and dissolved in simulated saliva pH 6.8 and 2 mL is taken and diluted with water up to 10 ml. The absorbance of the solution was measured at λ max 246 nm using UV/ visible spectrophotometer (Shimadzu). The percentage drug content was determined.

f) *In-vitro* dissolution studies

The release rate of Doxazosin mesylate fast dissolving Buccal strips were determined by using magnetic stirrer. The strips with 2×2 cm were placed in the 100mL of 6.8 pH simulated saliva as dissolution medium, and temperature was maintained at 37°C. From this dissolution medium, 2 mL of the sample solution was withdrawn at different time intervals. The samples were filtered through Whitman filter paper and absorbance was determined 300nm using double beam UV- Visible spectrophotometer.

g) Permeation study

The prepared Buccal strips were placed in the diffusion cell on the upper membrane of the (donor compartment) and the receptor compartment contain a simulated saliva (20 ml) it can be contact with the dialysis membrane upper side of the donor compartment contain a strips attach the strips of length and width (2×2) cm it contains 10mg of drug and the receptor compartment it contain a simulated saliva and magnetic bead and this diffusion compartment placed in the magnetic stirrer the drug permeation start through the dialysis membrane and enter in to the receptor compartment the drug to be enter in the receptor compartment and this solution taken 2ml at regular time intervals and maintain the sink condition by replace the 2ml of simulated saliva in to the receptor compartment and this every interval taken samples analyzed by (Shimadzu) UV-visible spectrophotometer.

h) Stability studies

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors. To assess the drug and formulation stability, stability studies were done as per ICH guidelines. The formulated Buccal strips were wrapped in aluminium foil and stored at 45 ± 0.5ºC for period of twelve weeks. After the period of three month, strips were tested for appearance, drug content and *In-vitro* drug release.

Determination of λ max of Doxazosin mesylate in ethanol

Accurately weighed quantity of 100 mg of Doxazosin mesylate was taken in 100 ml volumetric flask and it was dissolved in methanol and made up to 100 ml using ethanol.

Scanning: From the above stock solution, 10 µg/ml solution was prepared and scanned between 200-400 nm by keeping methanol as blank. The absorption maxima of 246 nm for Doxazosin mesylate was obtained and used for further studies.

Standard plot of Doxazosin mesylate in ethanol

Standard solutions of Doxazosin mesylate in methanol (10-80µg/ml) were prepared and measured at 246nm using UV-Spectrophotometer. The standard plot of Doxazosin mesylate was as shown in (Figure 1A). The obtained correlation coefficient was 0.9971 and the regression equation was used to calculate the concentration of unknown samples of Drug content estimation.

Preparation of calibration curve in using simulated saliva buffer pH 6.8

Accurately weighed quantity of 100 mg of Doxazosin mesylate was taken in 100 ml volumetric flask, make up to the volume with simulated saliva buffer pH 6.8 (stock I). Pipette out 5ml to 50ml volumetric flask (stock II). Preparing aliquots from stock II, 0.1, 0.2, 0.3, 0.4, 0.5, & 0.6ml.

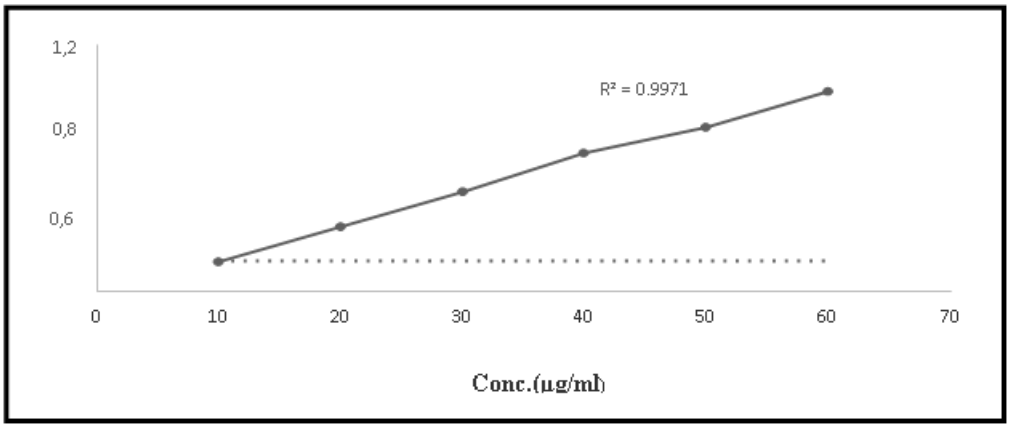

Figure 1: calibration curve in using simulated saliva buffer pH 6.8.

RESULTS AND DISCUSSION

Weight variation

The randomly selected strips strips about 2 × 2 cm areas were cut at different places from the casted strips and weight was measured. Weight of strips units varies from 43.36 to 55.33 mg. The proportion of carrier used have reduced the variation and improved the uniformity of the distribution in casted strips (Table No.3). It was observed that *in vitro* dissolving/disintegration time varies from 36 to 54 sec for all the formulations. *In vitro* disintegration time of strips s was affected by polymers viz. HPMC E 15, PVA and PVP. This is due to polymer's high-water absorption and retention capacities.

Drug content

The prepared strips formulations were studied for their drug content. The drug was dispersed in the range of 84 % to 98 %. Suggesting that drug was uniformly dispersed in all strips.

In vitro dissolution studies

The in-vitro drug release profiles of the formulations in simulated saliva pH 6.8 show differences depending on their composition. The rate of drug release from the HPMC E 15 strips was significantly higher than the strips containing PVP and PVA. The formulation F6 strips containing a HPMC E 15 showing high percentage of drug release (97.92%) within 12 mincompared to that of strips containing PVP and PVA as a polymer.

Pre-formulation Studies

Drugs-polymer interaction study by FT-IR spectrophotometer

An FT-IR spectroscopy study has been carried out separately to check the compatibility between the drug (Doxazosin mesylate) and the polymers (HPMC E15, PVP K30, PVA) used for the preparation of Drug and polymers. The FT-IR was performed for drug, polymers, and physical mixture of drug and polymers. The spectra obtained from FT-IR spectroscopy study at wave number from 4000 to 500 cm^{-1} are shown below.

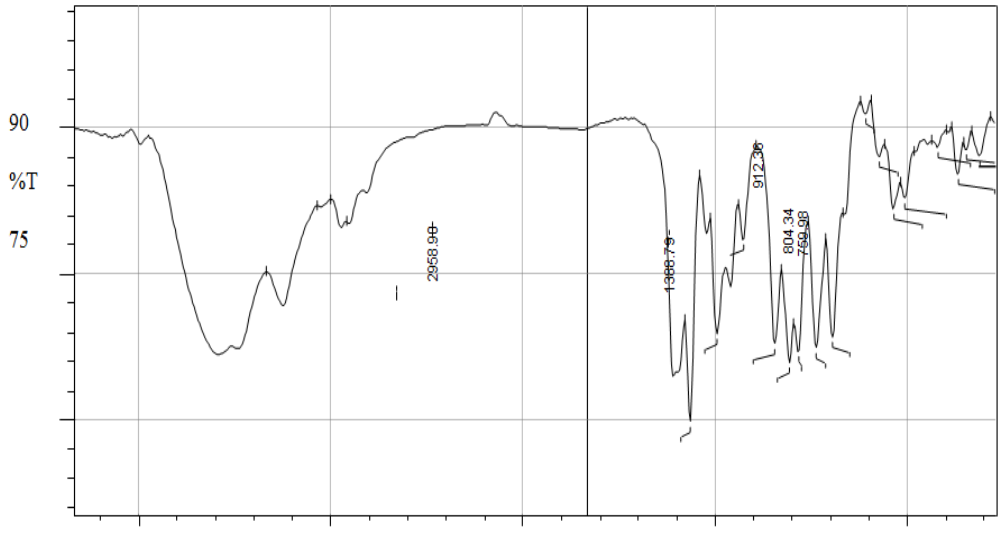

Figure 2: The FTIR spectrum of pure Doxazosin mesylate.

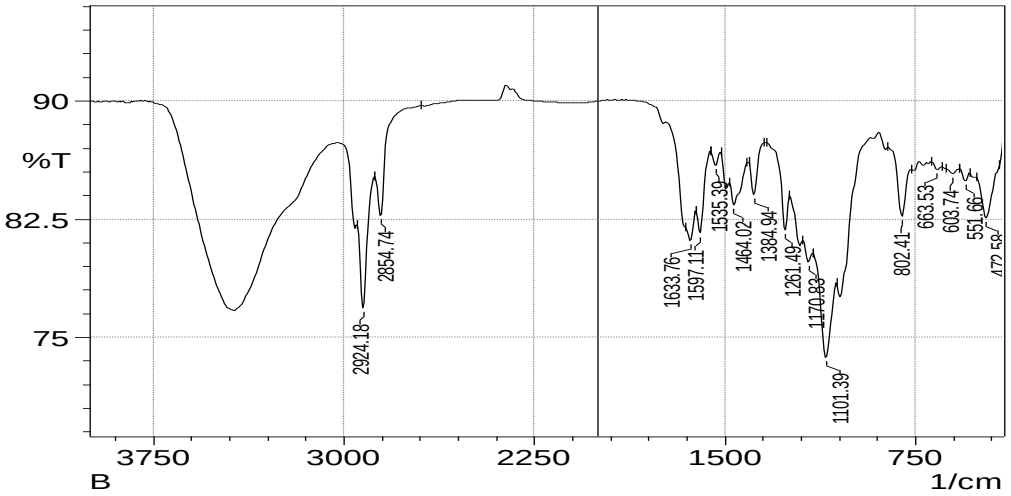

Figure 3: The FTIR Spectrum of DM+HPMCE15.

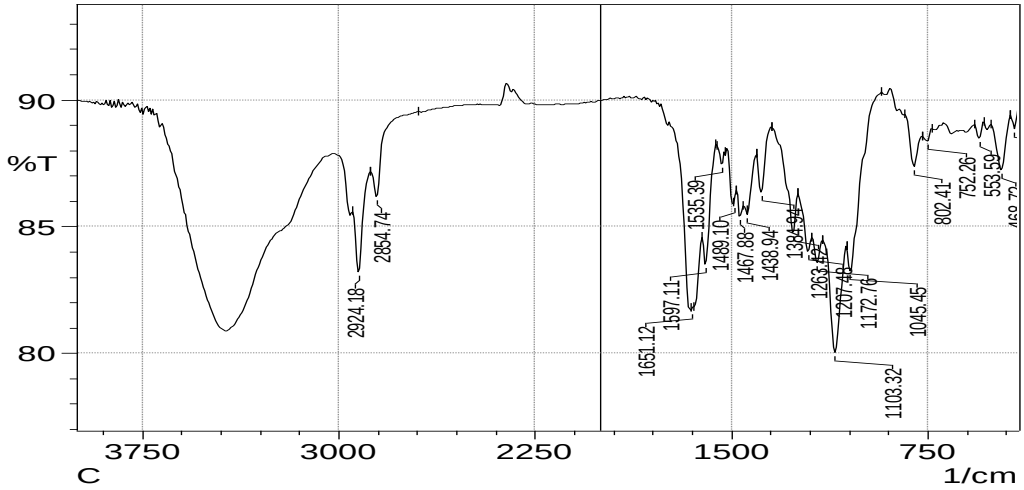

Figure 4: The FTIR Spectrum of Doxazosin + PVPK30.

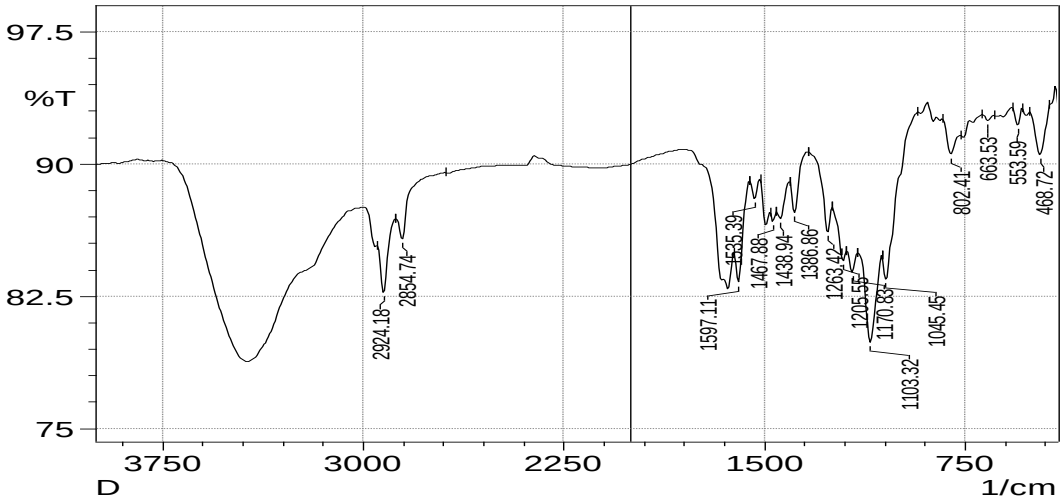

Figure 5: The FTIR Spectrum of Doxazosin +PVP.

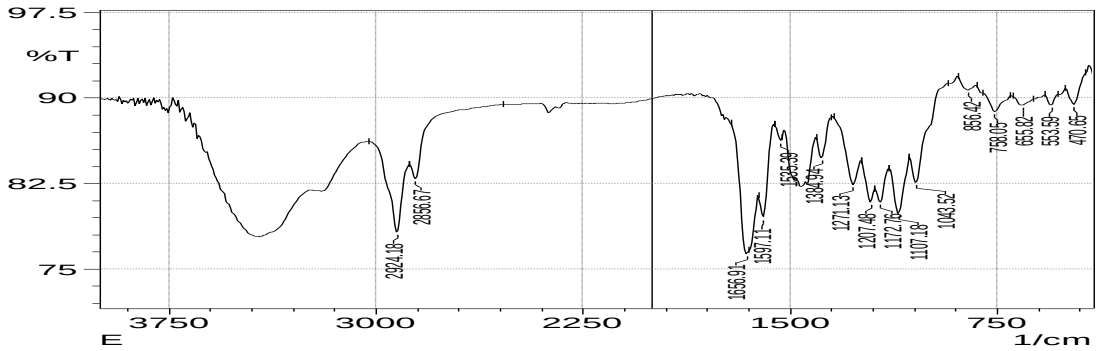

Figure 6: The FTIR Spectrum of Doxazosin+HPMCE15+PVP K30

Perusal to the above FTIR spectra, the characteristic peaks of Doxazosin mesylate of pure spectrum was retained in the FTIR spectra of physical mixture of drug with HPMC E15, PVA, PVP K30. Therefore, there was no drug polymer interaction is found. Hence, these polymers were used for the preparation of Buccal strips.

FTIR Interpretation

Table 2: Interpretation of FTIR spectrum of above figures.

SI. NO	Name of the Compound	Wave number (cm^{-1})	Functional group
1	Doxazosin mesylate	1101.39, 1174.69 1105.25, 1209.41, 1267.27 1388.79, 1491.02 1597.11	C-H stretch C-H inplane bendC-O-C stretch C-H bendN-H bend
2	DM: HPMC E15(1:1)	1101.39 1170.83 1261.49 1384.94 1597.11	C-H inplane bendC-O stretch C-O-C stretchC-H bend N-H bend
3	DM: PVP K30(1:1)	1045.45,1172.76 1103.32, 1207.48,1263.42 1384.94,1489.10 1597.11	C-O stretch C-H inplane bendC-O-C stretch C-H bendN-H bend
4	DM: PVA(1:1)	1045.45,1172.76 1103.32, 1207.48,1263.42 1384.94, 1597.11	C-O stretch C-H inplane bendC-O-C stretch C-H bendN-H bend
5	DM: HPMC: PVPK30 (F6)	1045.45,1172.76 1103.32, 1207.48,1263.42 1384.94, 1597.11	C-O stretch C-H inplane bendC-O-C stretch C-H bendN-H bend

Table 3: Weight uniformity of various Doxazosin mesylate fast dissolving oral strips.

Formulation code	Weight of strips (mg)			Averageweight (mg)±SD
	I	II	III	
F1	47.51	48.5	45.0	47.00±1.802
F2	55.50	56.5	54.0	55.33±1.258
F3	53.00	48.5	49.5	50.33±2.362
F4	47.50	46.5	45.2	46.40±1.153
F5	45.21	43.0	42.1	43.36±1.484
F6	55.21	52.0	52.1	52.36±1.484
F7	52.50	53.0	54.1	53.20±0.818
F8	48.00	49.1	50.1	49.06±1.050
F9	47.80	48.2	45.0	47.00±1.802

Results of Thickness Uniformity

Table 4: Thickness uniformity of various Doxazosin mesylate fast dissolving oral strips.

Formulationcode	Thickness of strips(mm)			Average thickness(mm)±SD
	I	II	III	
F1	0.12	0.14	0.16	0.14±0.020
F2	0.18	0.20	0.22	0.20±0.020
F3	0.25	0.13	0.16	0.18±0.062
F4	0.13	0.15	0.18	0.15±0.025
F5	0.22	0.22	0.25	0.23±0.017
F6	0.23	0.24	0.28	0.26±0.017
F7	0.22	0.24	0.21	0.22±0.015
F8	0.23	0.20	0.21	0.21±0.016
F9	0.21	0.22	0.21	0.21±0.015

Results of folding endurance

Table 5: Folding endurance of various Doxazosin mesylate fast dissolving oral strips.

Formulationcode	Folding endurance of strips			Average Folding endurance(mm)±SD
	I	II	III	
F1	345	343	344	344.00±1.52
F2	346	346	348	346.66±1.52
F3	350	352	351	351.00±1.03
F4	315	314	308	312.33±1.15
F5	351	357	351	353.00±1.52
F6	354	357	355	355.00±1.52
F7	310	310	312	310.66±1.15
F8	315	318	320	317.66±2.51
F9	322	323	320	321.66±2.31

Table 6: Disintegration study of various Doxazosin mesylate fast dissolving oral strips.

Formulations	Disintegration time (sec)			Average disintegrationtime(sec)±SD
	I	II	III	
F1	37	37	36	36.0±1.15
F2	41	44	44	42.0±1.15
F3	45	47	46	46.0±1.00
F4	39	32	34	35.0±1.00
F5	48	50	50	49.3±1.15
F6	58	52	54	54.3±1.15
F7	38	33	34	35.0±1.00
F8	48	50	48	48.6±1.15
F9	50	52	50	50.6±1.15

Table 7: Drug content uniformity of various Doxazosin mesylate fast dissolving oral strips.

Formulation Code	% Drug Content
F1	85.7±0.24
F2	84±0.15
F3	86±0.26
F4	94±0.12
F5	96±0.17
F6	98±0.22
F7	91±0.18
F8	90±0.34
F9	91±0.25

Table 8: *In vitro* release data of various Doxazosin mesylate fast dissolving oral strips.

Time(min)	Cumulative % Drug release				
	F1	F2	F3	F4	F5
2	22.00±0.02	40.00±0.25	50.00±0.16	54.00±0.24	40.00±0.24
4	22.22±0.12	40.40±0.27	50.50±0.28	60.54±0.23	51.42±0.22
6	23.44±0.13	60.8±0.15	61.00±0.18	66.14±0.21	70.07±0.12
8	39.67±0.25	71.40±0.21	76.60±0.14	71.79±0.16	75.92±0.18
10	61.06±0.17	77.10±0.19	83.35±0.21	78.49±0.22	76.00±0.24
12	61.66±0.19	77.85±0.26	84.66±0.16	85.25±0.19	79.52±0.22
14	71.26±0.14	78.60±0.22	85.00±0.18	88.07±0.24	81.52±0.12
16	72.95±0.23	78.70±0.19	85.01±0.14	93.91±0.11	87.52±0.18
18	73.65±0.25	78.90±0.26	85.5±0.21	94.07±0.24	89.25±0.24
20	73.05±031	80.14±0.22	85.88±0.16	95.91±0.11	91.47±0.22

Results of *In vitro* drug release study (F6-F9)

Table 9: *In vitro* release data of various Doxazosin mesylate fast dissolving oral strips.

Time (min)	% Cumulative drug release			
	F6	F7	F8	F9
2	42.00±0.24	40.92±0.11	40.48±0.17	41.80±0.15
4	65.42±0.22	48.77±0.23	50.96±0.14	50.98±0.21
6	86.07±0.12	55.81±0.15	55.82±0.26	58.04±0.15
8	97.92±0.18	62.47±0.13	62.92±0.24	65.16±0.23
10	-	68.74±0.14	70.08±0.19	68.54±0.22
12	-	70.11±0.19	75.10±0.23	70.80±0.25
14	-	70.50±0.23	76.24±0.24	75.72±0.16
16	-	70.58±0.22	80.37±0.23	76.78±0.18
18	-	75.01±0.23	82.04±0.24	78.29±0.17
20	-	77.65±0.88	84.45±0.23	80.25±0.25

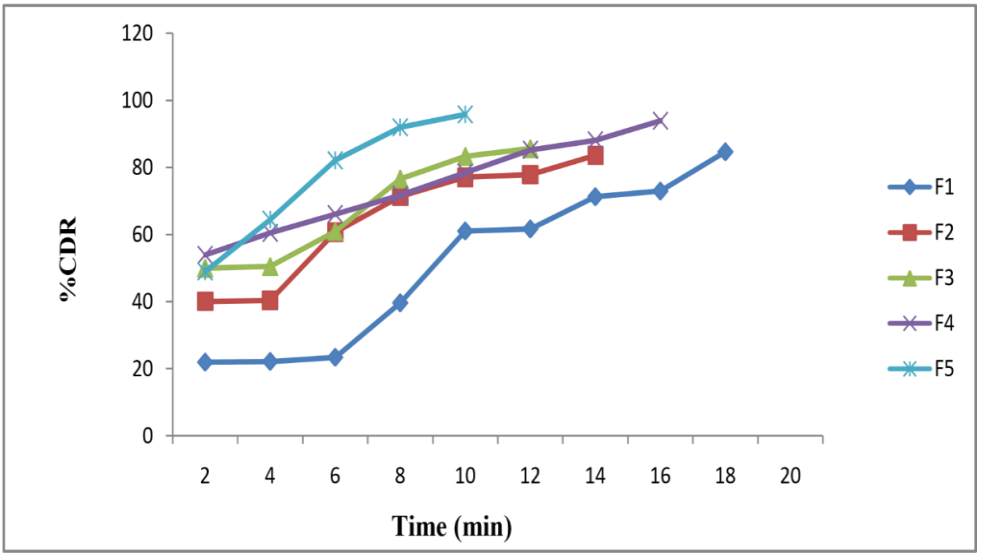

Figure 7: In-vitro drug release profile of formulations F1-F5.

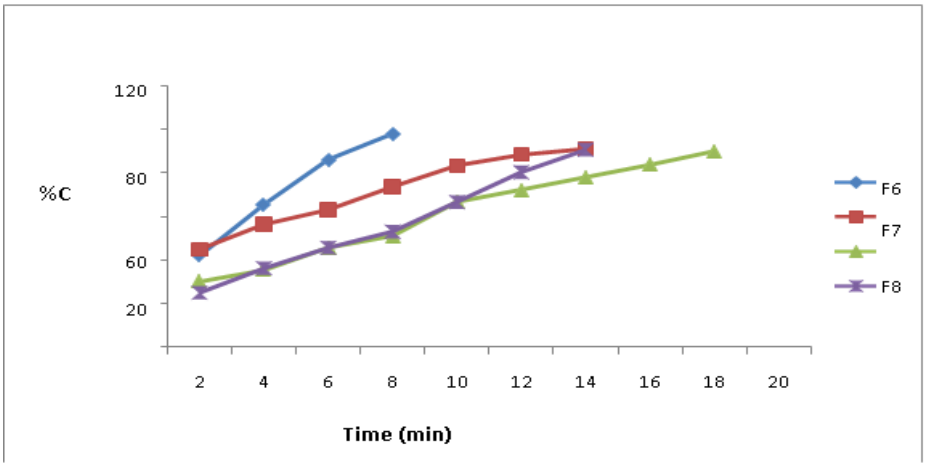

Figure 8: In-vitro drug release profile of formulations F6-F9.

Results of drug permeation study (F1-F6)

Table 10: Drug permeation study data of various Doxazosin mesylate fast dissolving oralstrips.

Time(min)	Permeation study				
	F1	F2	F3	F4	F5
5	48.4	37.4	41.8	39.6	36.6
10	51.04	42.14	50.98	46.56	50.16
15	55.9	53.52	56.28	52.7	62.04
20	65.2	60.6	60.30	56.252	78.86
25	74.58	64.66	65.68	64.672	90.6
30	79.64	70.512	71.1	72.284	92.2
35	84.3	79.932	78.764	83.04	-
40	-	83.712	85.61	89.488	-
45	-	-	-	93.348	-

Table 11: Drug permeation study data of various Doxazosin mesylate fast dissolving oralstrips.

Tim (min)	Permeation study			
	F6	F7	F8	F9
5	39.6	40.92	40.48	41.8
10	53.16	48.77	50.96	50.98
15	69.04	55.81	55.82	58.04
20	82.86	62.74	62.92	65.16
25	94.6	68.74	70.08	74.54
30	97.2	78.15	75.10	81.8
35	-	87.64	83.24	84.72
40	-	89.29	89.25	86.78
45	-			89.29

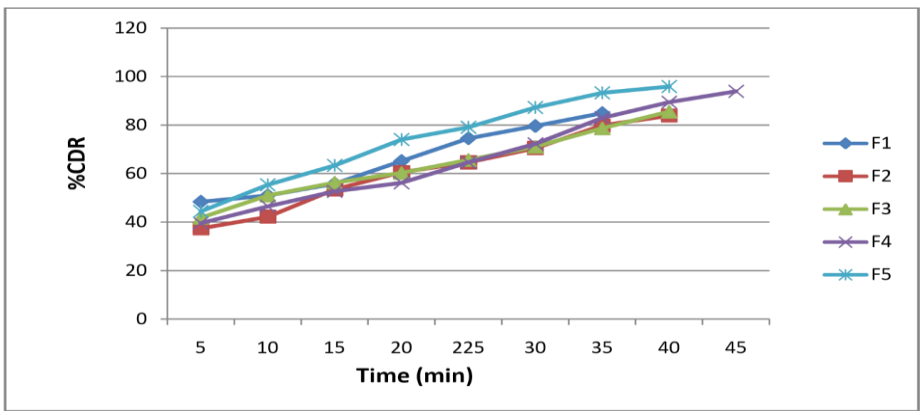

Figure 9: *In-vitro* permeation profiles of F1-F5.

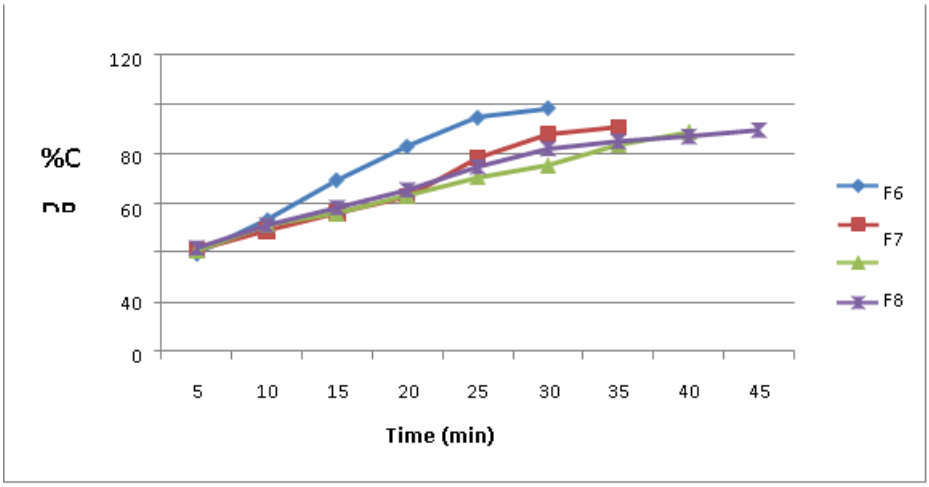

Figure 10: *In-vitro* permeation profiles of F6-F9.

Stability studies

Finally based on the thickness uniformity, weight uniformity, drug content uniformity, disintegration study, permeation study and in vitro drug release study confirmed that F6 was thebest formulation. For this strips drug content uniformity and stability studies were carried out.

The formulated strips F6 were stored at 40 ± 0.5 ºC in hot air oven, over period of three month. At the end of three month strips were tested for drug content and *in-vitro* release profiles. Stability studies were conducted as per ICH guidelines. Samples were taken at 30days intervals for drug content and *in-vitro* release estimation. The drug content and *in-vitro* release results were suggesting that there was no significant change in drug content and *invitro* drug release.

Table 12: Drug content data of stability study of formulation F6.

SL.NO	Trialno.	1st day	After 4 weeks	After 8weeks	After 12weeks
1	I	97.89±0.23	97.87±0.24	97.64±0.04	97.8±0.06
2	II	97.81±0.14	97.70±0.17	97.67±0.16	97.72±0.35
3	III	97.84±0.15	97.84±0.56	97.82±0.53	97.83±0.21
4	Mean	97.84±0.35	97.80±0.48	97.71±0.48	97.78±0.23

Table 13: *In-vitro* release data of stability study F6.

Time (min)	Cumulative % drug release			
	1St Day	After 4weeks	After 8 weeks	After 12 weeks
2	49.25	47.84	51.45	49.15
4	62.55	64.87	67.59	68.67
6	84.89	87.75	88.36	89.47
8	97.87	97.85	97.88	97.89

CONCLUSION

From the present research work that is "Formulation and evaluation of Doxazosin mesylate fast dissolving oral strips" for anti-hypertensive the following point were concluded

- In the beginning blank polymeric strips were prepared by solvent casting technique using HPMC E15, PVP K-30, PVA, the concentration of polymer was varied and the best formulations were chosen for incorporating the drug.
- The prepared strips were evaluated for following parameters like physical appearance and surface texture, weight uniformity, thickness of strips, folding endurance and drug content uniformity, disintegration, permeation study, drug excipients interaction studies, in vitro drug release and short-term stability studies.
- All the formulation showed acceptable quality control property formulation F6 having polymer concentration HPMC and PVP K30 (3:2) gave better drug release rate over period of 8 minutes thus formulation F6 was found to be the most promising formulation on the basis of acceptable evaluation property and the *invitro* drug release rate of 97.92%. Based on the FTIRstudies appear to be no possibility of interaction between the Doxazosin mesylate and polymers of other excipients used in the strips.
- Stability studies were conducted for the optimized formulation as per ICH guidelines for a period of 90 days which revealed that the formulation was stable. The result suggests that the developed fast release

strips of Doxazosin mesylate could perform the better than conventional dosage form leading to improved efficacy and better patient compliance.

ACKNOWLEDGEMENT

The authors are thankful to the management, Sree Siddaganga College of Pharmacy Tumkur for providing necessary facilities to carry out this work.

REFERENCE

1. Hagberg JM, Park JJ, Brown MD. The role of exercise training in the treatment of hypertension an update. Sports Med, 2000; 30(3): 193-206.
2. Carretero OA, Oparil S. Essential hypertension. Part I: definition and etiology Circulation, 2000; 101(3): 329-335.
3. Contreras F, Rivera M, Vasquez J, De la Parte MA, Velasco M. Diabetes and hypertension physiopathology and therapeutics. J Hum Hypertens, 2000; 14(1): 26-31.
4. Shojaei AH, 1998. Buccal mucosa as a route for systemic drug delivery: a review. J Pharm Pharm Sci, 1998; 1: 15-30.
5. Gupta Sachin, Srivastav Shruti, Vajpai Meenakshi *Journal of Pharmacy Research*, 2010; 3(4).
6. Betageri GV, Makarla KR. *Int J Pharm*, 1995; 126(1): 155-160.
7. Morris KR, Knipp GT and Serajuddin ATM *J. Pharm. Sci*., 1992; 81: 1185-1188.
8. Narang N, Sharma J. Sublingual mucosa as a route for systemic drug delivery.Int J Pharm Pharmaceut Sci, 2011; 3(2): 18-22.
9. Browhn GL. Formation of films from polymer dispersions. J Polym Sci., 1956; 22(102): 423-434.
10. Gavaskar B, Vijayakumar S, and Sharan G. "Overview on fast dissolving films." Int J pharm Pharma Sci, 2010; 2(3): 29-33.
11. Gohel M.C. "Development of taste masked film of valdecoxib for oral use." Ind J Pharma Sci, 2007; 69(2): 320-323.