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FORMULATION AND EVALUATION OF FAST DISSOLVING ORAL FILMS CONTAINING BENIDIPINE HYDROCHLORIDE

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1. ABSTRACT

The aim of this study was to formulate & evaluate fast dissolving oral films (FDOF's) containing benidipine hydrochloride (BEN), a calcium channel blocker used in the treatment of hypertension & angina pectoris. FDOF's offer several advantages over traditional dosage forms such as improved patient compliance, rapid onset of action & ease of administration without need of water. BEN was incorporated into the films using different polymers, such as HPMC E15, PVP-K30 & PVA to optimize the film properties and drug release profile. The films were prepared by solvent casting method & evaluated for various physicochemical properties, including thickness, weight variation, folding endurance, drug content uniformity & the in-vitro drug release. Among the 9 formulations, F3 formulation shows a rapid drug release 99.91% within 8 minutes. & it has drug content uniformity of 101.76%. The stability studies of the F3 formulation was also assessed under accelerated conditions ensuring their potential long-term storage. The results indicate the fast dissolving oral films of BEN offer an efficient patient friendly alternative to conventional oral dosage forms with potential for improved therapeutic outcomes in the management of hypertension.

KEYWORDS: Fast dissolving oral films, Hypertension, Benidipine hydrochloride.

2. INTRODUCTION

Hypertension is commonly known as high blood pressure, which is chronic medical condition characterized by elevated blood pressure levels persistently exceeding the normal range.[1] It's a significant global health concern affecting millions of people worldwide. It may be

influenced by genetic, lifestyle and environmental factors, often requires lifelong management to prevent complications. Despite the availability of various classes of antihypertensive medications, achieving and maintain the blood pressure levels can be challenging due to issues like pill burden, adverse effects and poor adherence. In this context, innovative drug delivery systems like fast dissolving oral films offer a promising solution by addressing some of these limitations In recent years, there has been growing interest in developing innovative drug delivery systems for improving the efficacy, safety and patient compliance of antihypertensive medications.[2] Among these advancements, fast dissolving oral films (FDOF) have emerged as a promising dosage form due to their numerous advantages such as rapid disintegration, ease of administration, and improved bioavailability.[3]

Benidipine hydrochloride, a third generation dihydropyridine calcium channel blocker, has emerged as a potent antihypertensive agent with additional benefits such as vasodilation and organ-protective effects.[4] It is used in the treatment of long term treatment of angina pectoris and hypertension.[5] The IUPAC name of Benidipine hydrochloride is 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridine-dicarboxylic acid methyl 1-(phenylmethyl)-3-piperidinyl ester hydrochloride.[6] Benidipine hydrochloride is stable to variations in heat, moisture and to the light exposure.[7] However, its conventional oral formulations may have limitations related to onset of action, variability in absorption and dosing frequency. FDOFs, rapidly disintegrate upon contact with saliva which has a rich blood supply and offer enhanced bioavailability due to their large surface area, provide an attractive alternative for delivering Benidipine.[8] The formulation of Benidipine FDOFs involves the incorporation of the drug into a thin film matrix composed of biocompatible polymers, plasticizers and other excipients by solvent casting method.[9] This process allows for precise dosing, uniform drug distributions and improved palatability compared to traditional dosage forms.[10] Additionally, FDOFs offer convenience of administration without the need of water, making them particularly suitable for the patients with swallowing difficulties or those who require discrete dosing.[11]

In this study, we have developed fast dissolving oral films of Benidipine HCl for better treatment of hypertension. HPMC E15 and PVA are used as film forming materials.

3. MATERIALS

Benidipine hydrochloride was procured from Yarrow chemicals Product Mumbai, India. HPMC E15 was purchased from Yarrow chemicals Mumbai. PVA and PVP K30 were purchased from SD fine chemical Laboratories Pvt. Ltd. All other chemicals used were of analytical grade.

4. METHODS

4.1. Preparation of standard and stock solutions

About 10 mg of Benidipine hydrochloride was accurately weighed and diluted in equal concentration of ethanol and phosphate buffer in 100 ml volumetric flask of concentration 100 µg/ml.

From the above solution 0.2, 0.4, 0.6, 0.8, 1.0, 1.2, 1.4 and 1.6 ml was pipetted out in 10 ml volumetric flask and diluted with the mobile phase which gives a required concentration of 2,4,6,8,10,12,14 and 16 µg/ml respectively.

4.2. Determination of absorption maxima

Various concentrationed samples were taken one by one and the maximum peak of UV graph was analyzed. From the UV spectrophotometric analysis, it was concluded that the benidipine drug showed a λ max at 263 nm. The observed λ max was used for further work to analyze the test samples.

4.3. Formulation of Benidipine hydrochloride fast dissolving oral films[12]

Benidipine hydrochloride fast dissolving oral films were prepared by solvent casting method. Polymers are dissolved in distilled water and Benidipine hydrochloride drug is dissolved in ethanol, which is poured into polymeric solution and stirred to form a homogenous solution for 15 minutes. Finally, plasticizer, sodium saccharin and citric acid were added to the solution and kept for stirring for 5 minutes. The solution was casted in mould 6 × 8 cm (length and width). Then kept in a hot air oven at 60°C for 2 hours. Thus, formed film was cut into size of 2*2 cm square films and conduct the evaluation studies.

Table 1: Formulation of fast dissolving oral films.

Formulation	F1	F2	F3	F4	F5	F6	F7	F8	F9
Benidipine HCl (mg)	48	48	48	48	48	48	48	48	48
HPMC E15 (mg)	250	300	350	100	100	100	---	---	---
PVP K30 (mg)	---	---	---	150	200	250	---	---	---
PVA (mg)	---	---	---	---	---	---	250	300	350
PEG 600 (ml)	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Sod, saccharin (mg)	2	2	2	2	2	2	2	2	2
Citric acid (mg)	2	2	2	2	2	2	2	2	2
Vanillin (mg)	1	1	1	1	1	1	1	1	1
Ethanol (ml)	5	5	5	5	5	5	5	5	5
Distilled water (ml)	5	5	5	5	5	5	5	5	5

5. CHARACTERIZATION OF ORAL FILMS

5.1. Physical appearance

The films were observed visually for their physical appearance such as colour, transparency and texture.

5.2. Weight variation

Four films (4 cm^2) of each batch of formulations were weighed individually and then together using the digital weighing balance. Individual weights of the films were noted down and average weight was calculated.

5.3. Thickness

The thickness of the film was measured using screw guage at three different places, averages of three values were calculated.

5.4. Folding endurance

It was determined by folding the films (2×2 cm) at the same place repeatedly until it was broken. The folding endurance was measured by calculating the number of times the film folded at the same place without breaking or cracking.

5.5. Drug content

The drug content was determined by dissolving the film of 4 cm^2 in 100 ml of phosphate buffer (pH 6.8) using magnetic stirrer for 30 minutes and drug content was evaluated spectrophotometrically at 263 nm and average was taken.

5.6. In vitro drug release

The drug release study was carried out using USP type 2 dissolution apparatus. The dissolution was carried out in 250 ml of phosphate buffer (pH 6.8) maintained at 37±0.5°C with 50 rpm. The samples (2ml) were taken at various time intervals and replaced with the same fresh buffer solution. The samples were filtered through whatmann filter paper, and analyzed by UV spectrophotometer at 263nm.[13]

5.7. Disintegration time

Disintegration test of films were carried out by petri dish method. In this method one film at a time was placed in petri dish containing a 5 ml of buffer and the time required to dissolve the film completely was measured. Estimation was carried out in triplicate.

6. RESULTS AND DISCUSSION

6.1. FTIR studies

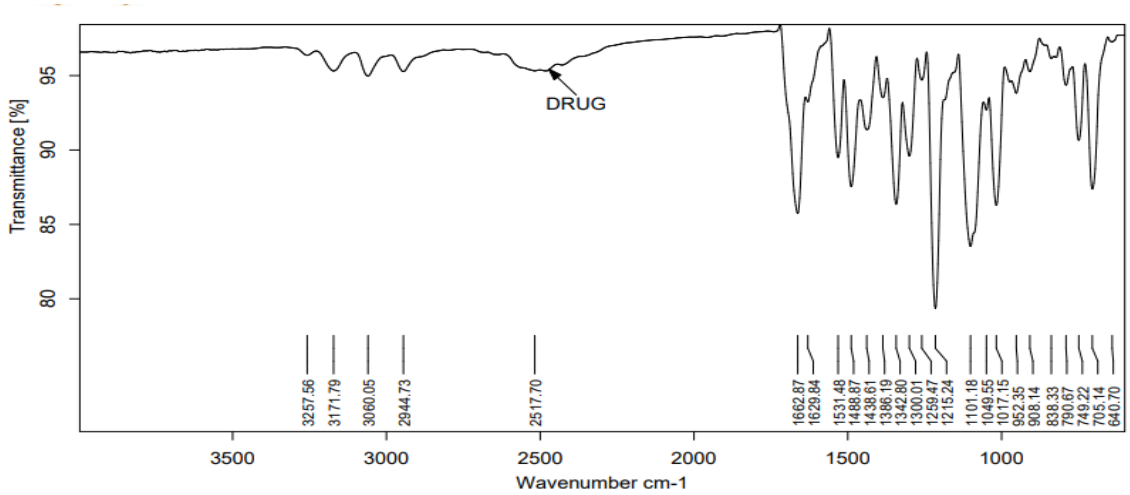

Figure 1: FTIR Study of pure drug.

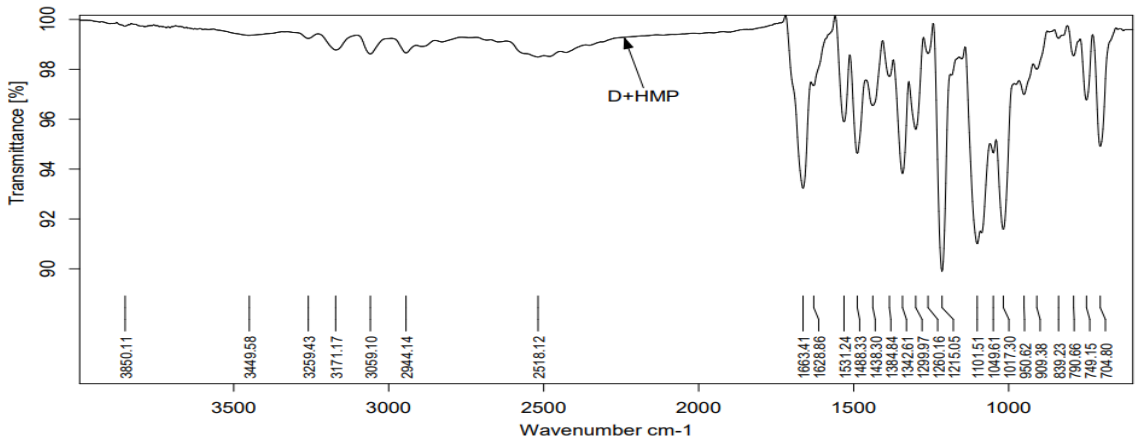

Figure 2: FTIR Study of drug + HPMC E15.

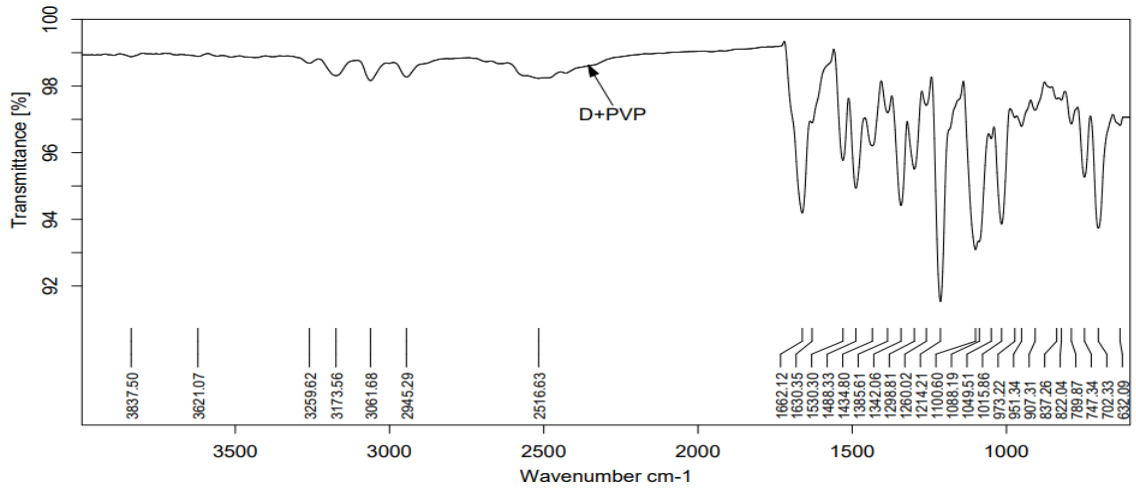

Figure 3: FTIR Study of drug + PVP K30.

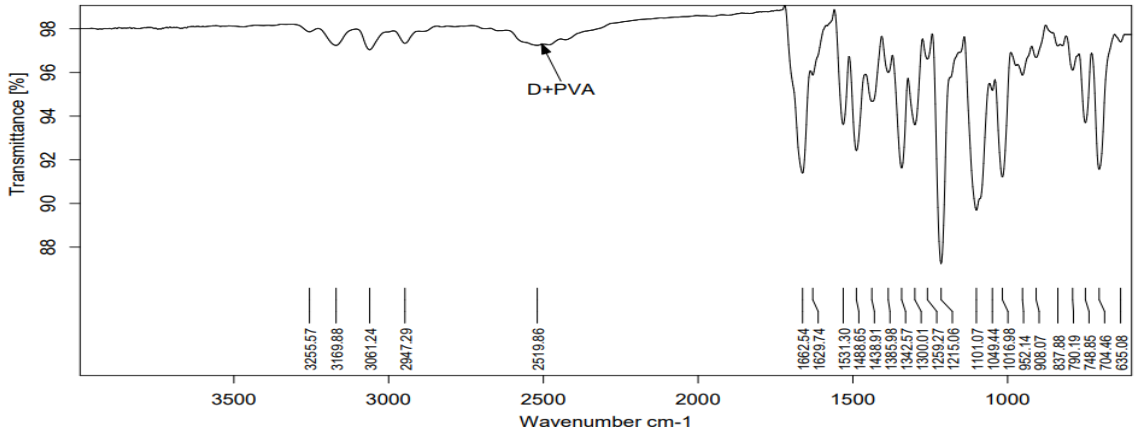

Figure 4: FTIR Study of drug + PVA.

6.2. Wavelength

The lambda max was observed at 263nm

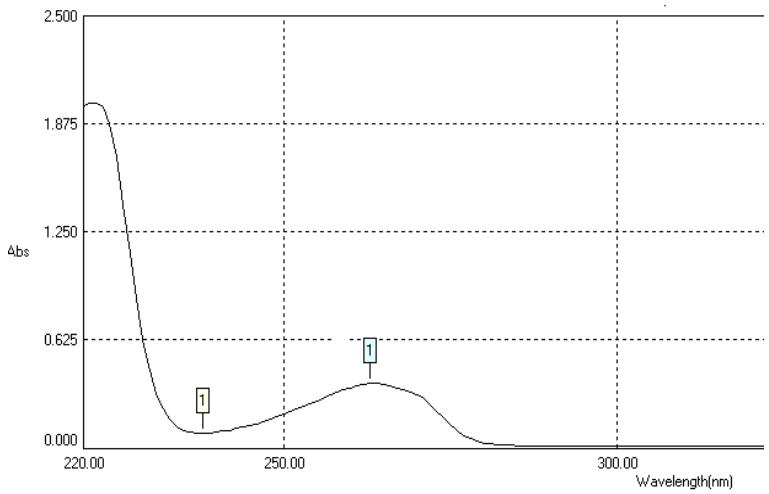

Figure 5: Wavelength of Benidipine hydrochloride.

6.3. Standard graph

Table 2: Standard graph.

Concentration (µg/ml)	Absorbance @ 263nm
2	0.110
4	0.206
6	0.297
8	0.412
10	0.490
12	0.606
14	0.734
16	0.844

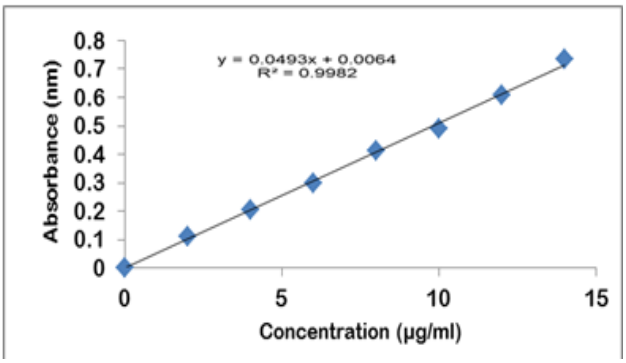

Figure 6: Standard curve of Benidipine HCl.

6.4. Characterization of Benidipine HCl films

Total nine formulations were prepared and subjected to different evaluation parameters. Among these formulations, F3 shows good results. The appearances of films were evaluated by visual examination such as transparent and opaque. The films were thin, flexible, elastic, smooth and transparent (figure 7).

Figure 7: Appearance of film.

The weight variation ranged between 24.2±0.32 and 34.6±0.75 showed that there was no significant difference in the weight of films. This ensured the uniformity of the films.

The thickness of all the formulations was varied from 0.20±0.01 and 0.24±0.03 and ensured the uniformity of films.

The films were subjected to folding endurance to evaluate the flexibility studies. All the formulations showed >150. This revealed that the prepared films were having capacity to withstand the mechanical pressure along with good flexibility.

Table 3: Evaluation parameters of Benidipine HCl oral films.

Formulations	Weight uniformity (mg)	Thickness (mm)	Folding endurance	Disintegration time (sec)	Drug content (%)
F1	24.2±0.32	0.20±0.02	245.33±1.24	36.67±0.58	99.68±0.64
F2	31.1±1.34	0.22±0.02	217.67±2.05	40.67±1.53	100.51±0.24
F3	34.2±0.69	0.20±0.01	253.30±1.00	34.67±0.58	101.76±0.24
F4	24.6±0.65	0.22±0.01	219.33±1.53	39.67±2.08	97.46±0.42
F5	30.3±0.49	0.24±0.02	254.33±2.52	49.00±1.00	98.01±0.24
F6	34.5±0.49	0.24±0.03	252.00±2.65	54.67±2.08	96.76±0.24
F7	24.7±1.34	0.21±0.02	272.33±1.53	35.67±2.08	95.93±0.24
F8	30.3±1.27	0.23±0.03	223.33±2.52	49.33±1.15	98.43±0.24
F9	34.6±0.75	0.27±0.01	272.33±2.08	51.33±2.08	100.10±0.64

n = 3 ± SD

The percentage of drug content in various formulations were ranged from 95.93±0.24 and 101.76±0.24%.

The in-vitro disintegration time studies suggested that films prepared by using all the grades of polymers showed the disintegration time below 54 sec and was in acceptable range.

A rapid dissolution of all the films was observed by the dissolution test, in which above 90% of Benidipine hydrochloride was released within 10min. The formulation F3 showed maximum drug release (99.91±0.48) within 8 minutes.

Table 4: In-vitro drug release data.

Time (sec)	F1	F2	F3	F4	F5	F6	F7	F8	F9
2	31.76	30.89	38.81	28.98	32.10	36.52	29.03	28.5	33.75
4	48.14	62.01	69.43	39.65	42.91	51.59	40.42	43.32	45.00
6	66.23	85.44	90.05	47.01	50.08	68.25	51.88	61.26	63.02
8	79.06	97.28	99.91	63.62	65.63	80.26	74.93	71.68	80.71
10	90.44			76.86	79.43	92.97	89.17	90.95	92.93
12	100.04			90.79	96.25	101.09	97.99	100.08	102.15

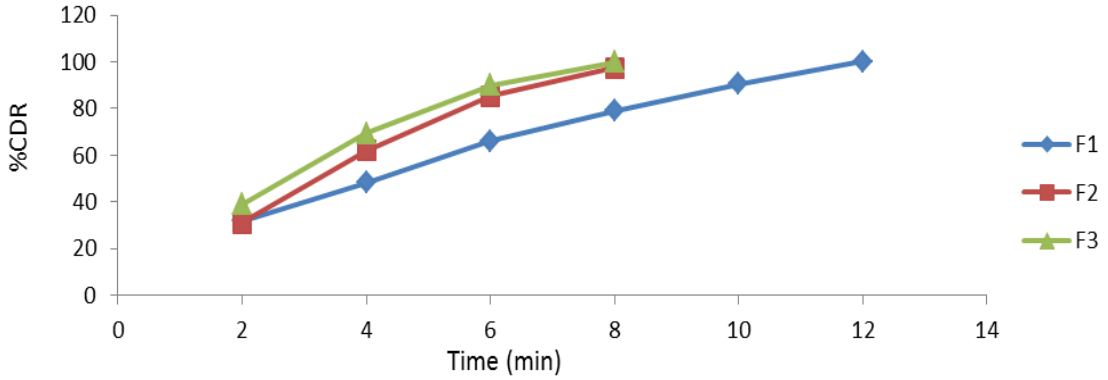

Figure 8: In –vitro drug release of formulations F1-F3.

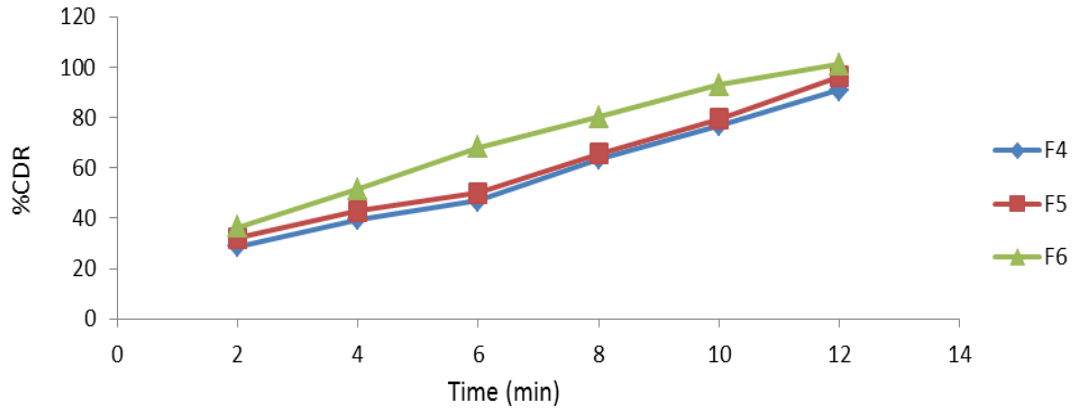

Figure 9: In-vitro drug release of formulations F4-F6.

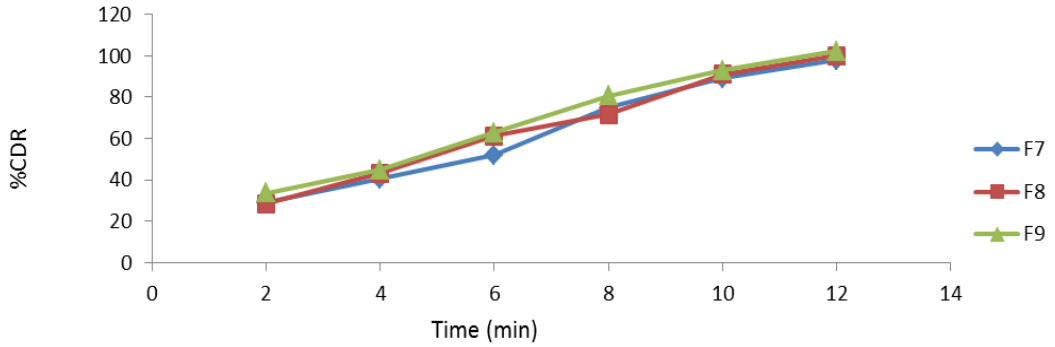

Figure 10: In-vitro drug release of formulations F7-F9.

Stability studies

Finally based on the thickness, weight uniformity, drug content uniformity, disintegration study and *in-vitro* drug release study confirmed that F3 was the best formulation.

The formulated films F3 were stored over period of four weeks. At the end of four weeks films were tested for drug content and *in-vitro* release profiles. Stability studies were

conducted as per ICH guidelines. Samples were taken at 30 days 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 *in-vitro* drug release.

Table 5: Drug content of optimized formulation (F3) on 1st day and 4th week.

SL.NO	Trial no.	1st day	After 4 weeks
1	I	100.79	97.88
2	II	100.38	98.71
3	III	100.79	99.54
4	Mean	100.65±0.24	98.71±0.83

Table 6: *In-vitro* release drug release data for optimized formulation (F3).

Time (min)	% cumulative drug release	
	1st Day	After 4weeks
2	39.01±0.75	37.98±0.46
4	70.58±0.93	69.23±0.47
6	90.05±0.77	88.15±0.93
8	99.91±0.86	97.04±0.52

CONCLUSION

Fast dissolving oral films containing Benidipine hydrochloride were developed by using various types of polymers such as HPMC E15, PVA and PVP K30 by solvent casting method, to overcome the first-pass metabolism and the subsequent low bioavailability of the drug. The method of formulation was found to be modern and economic. Among all the nine formulations, F3 was found as a best formulation which contains Benidipine and HPMC E15, showed a excellent film forming characteristics such as disintegration time 34 sec and percentage drug release was 99.91 % within 8 minutes.

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