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Benidipine hydrochloride fast dissolving sublingual film formulation and evaluation for the treatment of hypertension

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Abstract
The sublingual route is extremely beneficial for a rapid onset of action and improved patient compliance. It increases drug utilization and active pharmaceutical ingredient efficacy. Patients prefer the oral route the most. A fast-dissolving oral drug delivery system is a solid dosage form that dissolves or disintegrates in the mouth in seconds without using water or chewing. The drug's solubility and bioavailability were improved by using solid dispersion. Physical mixture was used to create solid dispersions of Benidipine hydrochloride: β-cyclodextrin in various ratios (1:1, 1:2, 1:3, 1:4). The current study discusses the formulation aspects, manufacturing methods such as solvent casting, evaluation parameters, and applications of fast dissolving films made from polymers such as HPMC E-5, as a film forming agent, Sodium starch glycolate, as a super disintegrating agent, Critic acid, as a saliva stimulating agent, PEG 400 as a plasticizer, and Mannitol as a sweetener. This study concluded that the fast-dissolving sublingual film of Benidipine Hydrochloride performed better than the marketed formulation, and all parameters performed satisfactorily.

Keywords: Sublingual route, Benidipine hydrochloride, β-cyclodextrin, HPMC E-5, Sodium starch glycolate, PEG 400

Introduction

Sublingual refers to the area under the tongue. It refers to a technique for giving medication orally so that, as opposed to passing via the digestive system, the medication quickly enters systemic circulation through a highly vascularized sublingual pathway in the oral mucosa.

All age groups experience dysphagia (difficulty swallowing), but it is particularly challenging for the elderly, kids, and patients who are mentally challenged, uncooperative, queasy, or on low liquid intake diets to swallow these dose forms. The medication is taken sublingually, which means it is inserted beneath the tongue and immediately enters the bloodstream [1].

The main mechanism for drug absorption in the oral mucosa is passive diffusion into the lipoidal membrane. Sublingual absorption of the drug is 3 to 10 times greater than oral absorption and is only surpassed by hypodermic injection. For these formulations, a small amount of saliva is usually enough to cause tablet disintegration in the oral cavity. Sublingual films have been developed to solve the problems associated with traditional oral dosage forms and to improve the bioavailability optimization of therapy. This overview provides a comprehensive representation of sublingual drug delivery systems, including benefits and drawbacks, various dosage forms and their formulation parameters, commonly used super disintegrants, evaluation, and some commercially available sublingual dosage forms [2].

Solvent casting techniques are the most favored technique for making a fast-dissolving film. Hypertension, a prevalent cardiovascular condition, is a significant risk factor for coronary artery disease. The medical term for high blood pressure is hypertension (HTN) (BP). The prerequisites for it to exist are systolic blood pressure (SBP) > 140 mmHg and diastolic blood pressure (DBP) > 90 mmHg [3]. Hypertension, a well-recognized public health problem, is one of the major causes of death from cardiovascular illnesses (CVD) like heart failure, coronary heart disease, myocardial infarction, and stroke. According to the World Health Organization (WHO) and the International Society of Hypertension (ISH), hypertension accounts for 4.5% of the worldwide disease burden in 2003. It is as prevalent in many developing countries as it is in the affluent world [4].

According to the World Health Organization, almost 1 billion people in both developed and developing countries have hypertension that is below the 140/90 mmHg limit. Hypertension is the third most common cause of death, accounting for 4 million deaths annually and 1 in 8 fatalities worldwide. Benidipine Hydrochloride Sublingual Film can be used to treat hypertension right away [5].

Material and methods

Materials and reagents Benidipine Hydrochloride were obtained from Prayosha Health Care. Pvt. Ltd., Gujarat. HPMC E5, PEG 400, Citric acid, β-cyclodextrin, Mannitol, and Sodium starch glycolate were purchased from Lobachem Pvt. Ltd., Mumbai, and Ethanol was obtained by Changshu Hongsheng Fine Chemical Co., Ltd., Ghaziabad.

Drug Excipients Compatibility Study

The FTIR spectra of the medication and its blend with excipients in a 1:1 ratio was both captured on the (Shimadzu instrument). Using an FTIR spectrophotometer, the materials were scanned using the KBR disc method between 4000 and 400 cm-1. The various functional groups contained in the samples were identified by comparing the peaks to the IR tables [6].

Formulation of Sublingual Film containing Benidipine Hydrochloride

The fast-dissolving sublingual film of the solid dispersion of benidipine hydrochloride was made utilizing the solvent casting process and HPMC as the film-forming polymer, PEG 400 as the plasticizer, citric acid as the saliva stimulant, mannitol as the sweetener, and sodium starch glycolate as the super disintegrating agent. The formulation

was created using the table's composition as a guide. PEG 400 was added to the hydrophilic polymer HPMC after it had been accurately weighed, dissolved in distilled water, and stirred on a magnetic stirrer for two hours. Additionally, sodium starch glycolate, citric acid, and mannitol were dissolved in distilled water in another beaker and added to the polymeric solution (a solution which contains HPMC and PEG 400). The medicine (benidipine hydrochloride) was added in the correct quantity and agitated thoroughly for 30 minutes to ensure proper mixing before being added to the homogenized solution with a magnetic stirrer. In order to de-aerate the solution, it was left to stand for 12 hours. After that, the mixture was placed in a petri dish and left at room temperature for 10–12 hours. Films were removed and cut into 2 cm2 squares after drying. The sample was kept in a desiccator with a 60.5% relative humidity and a temperature of 30°C [7].

Evaluation Parameter of Sublingual Films The thickness of films

A micrometer screw gauge was used to measure the film's thickness three times. Calculated 8 were the averages of the three values [8].

Weight variation

The weight variation of the fast-dissolving sublingual film of size 2x2cm2 was cut, and three films of each formulation were taken and individually weighed using an electronic scale. The typical weight was determined [9].

Folding endurance

A small film of 2×2cm2 was subjected to this test by folding the film at the same plane repeatedly several times until a visible crack was observed. The number of times the film could be folded at the same place without breaking/cracking gave the value of folding endurance [10].

Surface pH

A pH meter was used to calculate the surface pH. The film was tested by being placed in a petri dish. After that, it was given 0.5 ml of phosphate buffer to moisten and was left for 30 seconds. After touching the electrode of the pH meter to the formulation's surface and giving it a minute to equilibrate, the pH was measured. For each formulation, the average of three determinations was calculated.

% Drug content

The film (size 2x2 cm^2) was trimmed and set aside. The volumetric flask was used, 100 ml of phosphate buffer pH 6.8 was added, and the film was then dissolved in the phosphate buffer pH 6.8. For ten minutes, the volumetric flask was continually shaken. After that, Whatman filter paper was used to filter the solution. Following filtering, 1 ml of the aforementioned solution was taken out and diluted with phosphate buffer pH 6.8 to a volume of 10 ml in a volumetric flask. At 239.3 nm, the solution was examined using a UV spectrophotometer. To determine the amount of drug present in the film [11].

***In-vitro* disintegration time**

A petri dish containing 6 ml of phosphate buffer pH 6.8 was used to measure the amount of time it took for a fast-dissolving sublingual film (2 x 2 cm2) to dissolve. The length of time needed for the film to completely degrade was noted [12].

***In-vitro* % drug release**

Benidipine Hydrochloride's fast-acting sublingual film's in-vitro drug release was investigated utilising a USP dissolution equipment II (Paddle type) and phosphate buffer pH 6.8 (250 ml) as the dissolution medium. A piece of metal wire slab with a surface area of 2x2 cm^2 was cut, fastened to the film, and placed at the base of the dissolving tank. With the paddle rotating at 50 rpm, the temperature was kept at 37 0.5 ^oC. To maintain the volume of the dissolution media, the 5ml sample was removed at predetermined intervals and replaced with an equal volume of phosphate buffer pH 6.8. The sample was promptly filtered through Whatman filter paper, and the drug concentration was determined using a UV spectrophotometer at 239.3 nm.[13].

Table 1: Preparation of trial batches

Batch no. Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Solid dispersion of Benidipine Hydrochloride (1:4) (mg)	335	335	335	335	335	335	335	335	335
HPMC E5 (mg)	600	650	700	600	650	700	600	650	700
Sodium starch glycolate (mg)	8	8	8	12	12	12	16	16	16
PEG-400(ml)	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06
Citric acid (mg)	10	10	10	10	10	10	10	10	10
Mannitol (mg)	20	20	20	20	20	20	20	20	20
Distilled water(ml)	30	30	30	30	30	30	30	30	30

Result and discussion

Preparation of standard Calibration curve of Benidipine Hydrochloride: Benidipine Hydrochloride showed maximum absorption at wavelength 239 nm in phosphate buffer pH 6.8. A standard curve was plotted by taking the absorption of diluted stock solutions (5, 10,15, 20, 25, µg /ml) at wavelength 239 nm.

Table 2: Calibration curve readings (conc. vs. abs)

Concentration (µg/ml)	Absorbance Mean± SD
0	0
5	0.3553±0.003
10	0.7407±0.009
15	0.9946±0.006
20	1.2623±0.012
25	1.4963±0.018

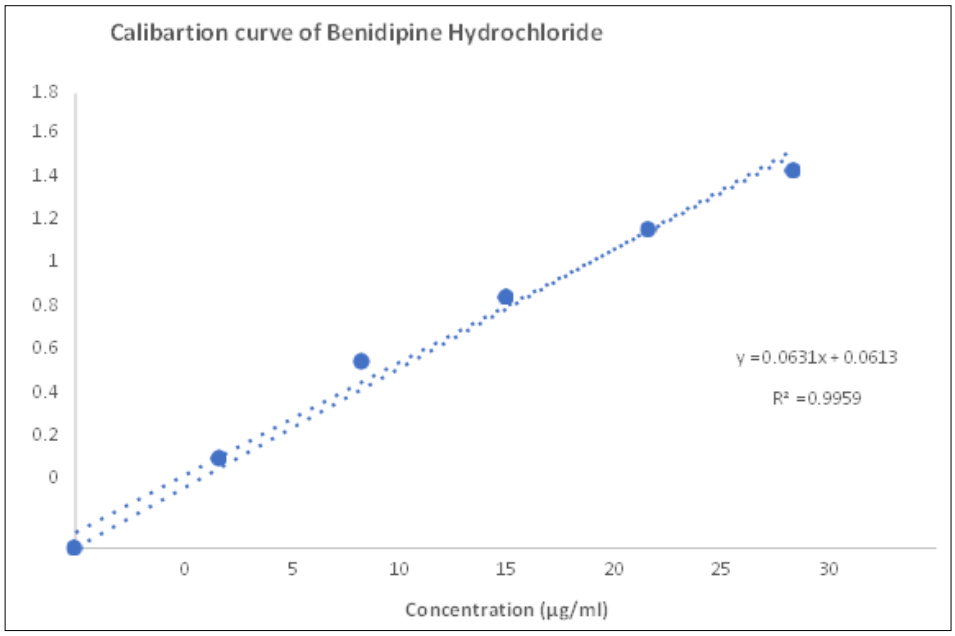

Fig 1: Calibration curve in Benidipine Hydrochloride

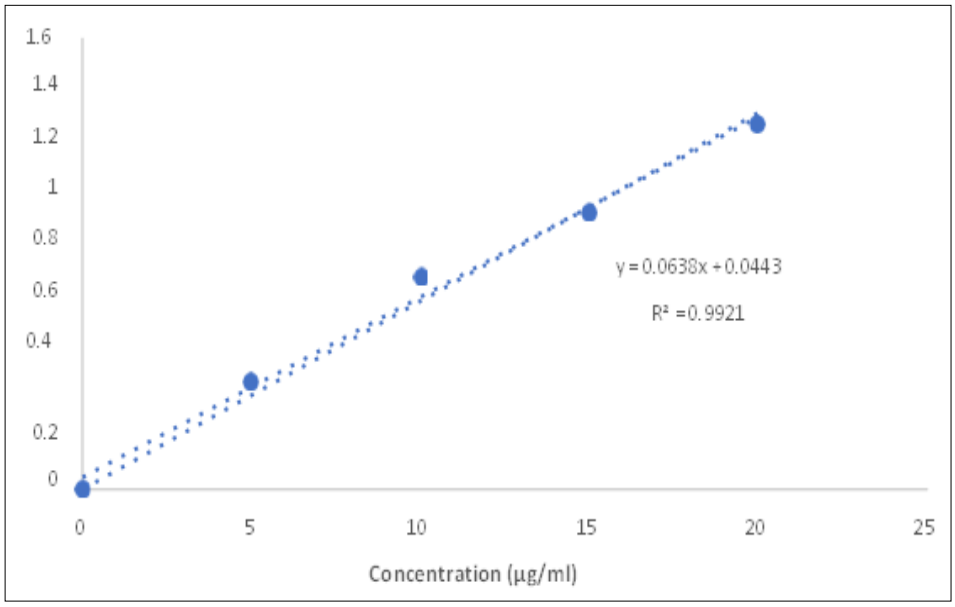

Fig 2: Calibration curve of Benidipine Hydrochloride and Benidipine Hydrochloride in phosphate buffer pH 6.8

Preparation of Solid Dispersion of Benidipine Hydrochloride with β- Cyclodextrin

The solid dispersion of Benidipine Hydrochloride with β-cyclodextrin (1:1, 1:2, 1:3, 1:4) in distilled water and phosphate buffer pH 6.8 was performed and the results were obtained in (1:4).

FITR Results

FTIR spectrum of Benidipine Hydrochloride, physical mixture of Benidipine Hydrochloride with HPMC-E5, solid dispersion of Benidipine Hydrochloride with β-cyclodextrin, physical mixture of HPMC-E5 with Benidipine Hydrochloride and β-cyclodextrin solid dispersion was recorded and it was found in accordance with the reported peaks shown in figures. FTIR spectrum of the physical mixture of Benidipine Hydrochloride with HPMC-E5 showed the major peaks of both components. There was no incompatibility or interaction found between Benidipine Hydrochloride and HPMC-E5 in their physical mixture. FTIR spectrum of solid dispersion of Benidipine Hydrochloride with the β-cyclodextrin showed the major peaks of both components. There was no incompatibility or interaction found between Benidipine Hydrochloride and β-cyclodextrin in their solid dispersion form.

FTIR spectrum of the physical mixture of HPMC-E5 with Benidipine Hydrochloride and β-cyclodextrin solid dispersion showed the major peaks of both the component. There was no incompatibility or interaction found between Benidipine Hydrochloride and β-cyclodextrin solid dispersion with HPMC-E5 in their physical mixture.

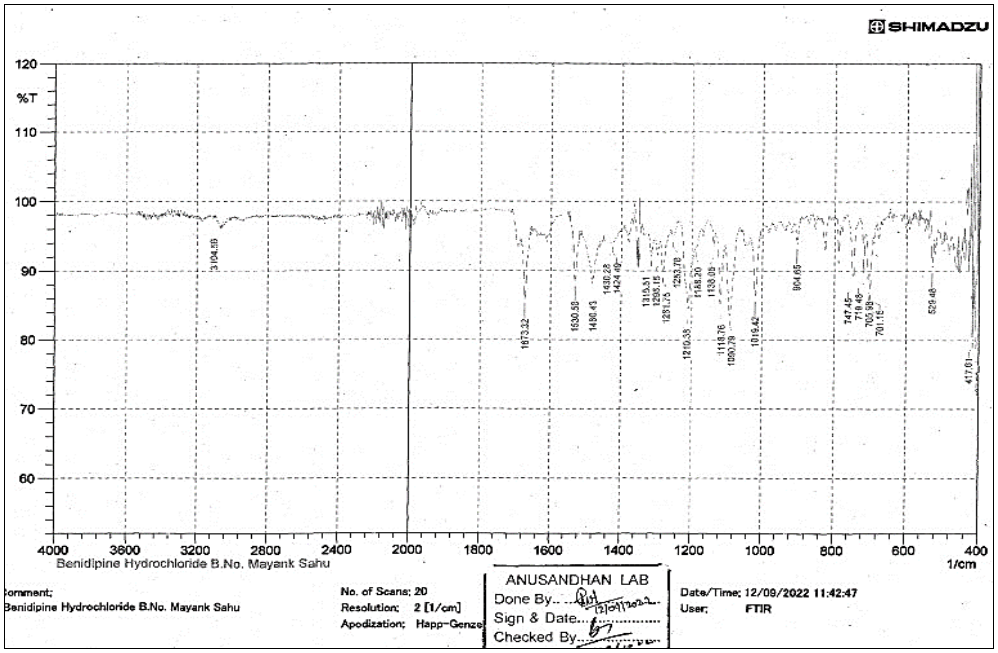

Fig 3: FTIR spectrum of Benidipine Hydrochloride

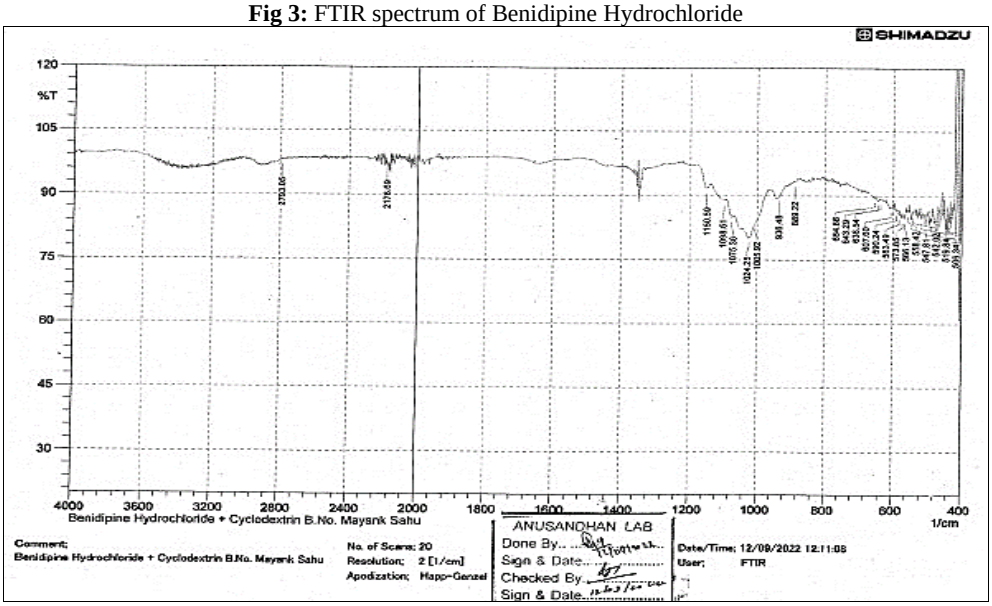

Fig 4: FTIR spectra of Benidipine Hydrochloride and β-cyclodextrin solid dispersion

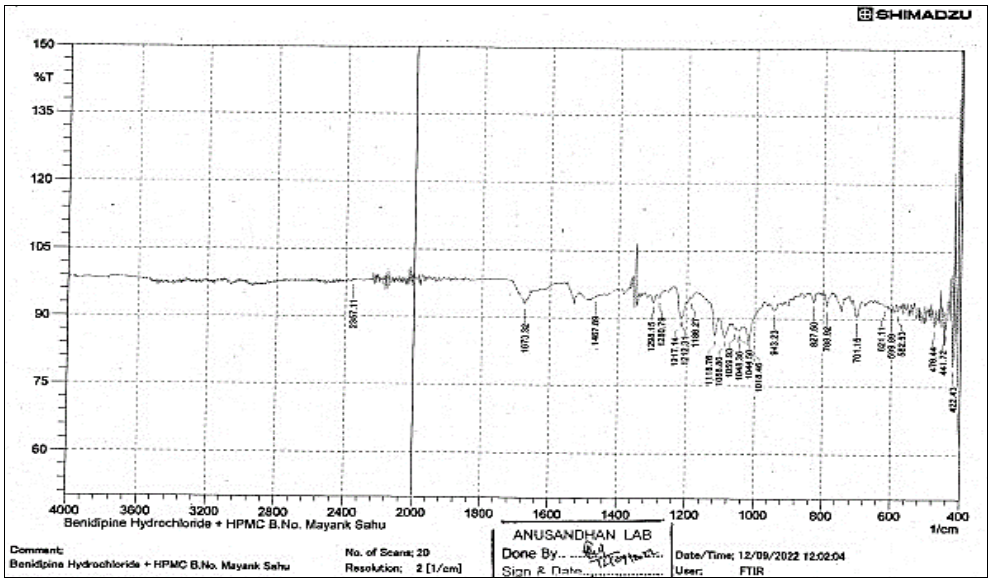

Fig 5: FTIR spectrum of physical mixture of Benidipine Hydrochloride and HPMC-E5

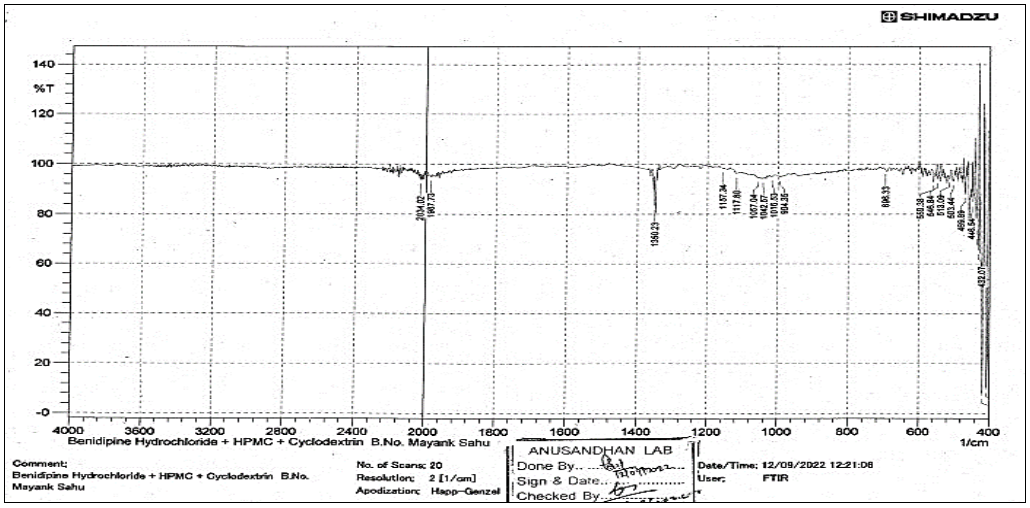

Fig 6: FTIR spectrum of HPMC-E5 with Benidipine Hydrochloride and β-cyclodextrin solid dispersion

Discussion of Evaluation Parameters of Fast dissolving Sublingual Film

Thickness of film

Each film is the same thickness throughout. The average thickness of all the film formulations was found to be in the range of 0.08±0.01 to 0.12±0.03 mm.

Weight variation

Drug-loaded films (2x2 cm2) were analyzed for weight uniformity. The films were found to be uniform. The weight of film formulations was found to be in the range of 59.15±0.02 to 72.12±0.04 mg.

Folding endurance

A small film of 2×2cm2 was subjected to this test by folding the film at the same plane repeatedly several times until a visible crack was obtained. The folding endurance of the film was found to be in the range of 106 to 154 times.

Surface pH

The surface pH was determined by using a pH meter. This test was evaluated by placing the film in a petri dish. Then it was moistened with 0.5 ml of phosphate buffer and kept for the 30s. The pH was noted after bringing the electrode of the pH meter in touch with the surface of the formulation and allowing equilibration for 1 min. The surface pH of the film was found to be in the range of 6.4 to 6.8 pH.

% Drug content

The drug content of all batch formulations was calculated by using size (size 2×2 cm2). Each formulation's three trials were analyzed spectrophotometrically. All of the formulations' means and standard deviations are calculated. The % drug content of the film was found to be in the range of 86.16±1.15 to 96.82±0.68.

***In-vitro* disintegration time**

The disintegration time of fast dissolving sublingual film was measured by placing the film (2×2cm2) in a petri dish containing 6 ml phosphate buffer pH 6.8. The *In-vitro* disintegration time of the film was found to be in the range of 23±0.22 to 30±0.42.

Table 3: Evaluation data of various parameters.

Formulation	Thickness (mm) Mean± SD	Weight variation (mg) Mean± SD	Folding endurance (Times)	Drug Content (%) Mean± SD	Surface pH	Disintegration Time (sec) Mean± SD
F1	0.08±0.01	59.15±0.02	106	93.23±1.60	6.41	23±0.22
F2	0.09±0.03	62.38±0.03	111	91.59±1.42	6.62	22±0.36
F3	0.08±0.02	65.26±0.05	137	88.14±1.32	6.83	25±0.27
F4	0.10±0.04	61.43±0.01	134	93.21±0.52	6.86	19±0.34
F5	0.07±0.03	63.52±0.02	141	86.16±1.15	6.65	23±0.94
F6	0.10±0.02	66.35±0.04	128	81.36±1.74	6.88	28±0.40
F7	0.11±0.03	62.62±0.05	149	91.73±1.76	6.98	26±0.22
F8	0.12±0.03	67.22±0.07	154	96.82±0.68	6.86	29±0.16
F9	0.12±0.02	72.12±0.04	123	87.53±0.83	6.48	30±0.42

***In-vitro* % drug release**

In-vitro % drug release of fast dissolving sublingual film was measured by using USP dissolution apparatus II (Paddle type) in phosphate buffer pH 6.8 (250 ml) as the dissolution medium. The film of area 2×2 cm2 was cut and fixed to a piece of metal wire slab and placed at the bottom of the dissolution vessel. The temperature was maintained at 37±0.5ºC with paddle speed rotation at 50 rpm. The *In-vitro* % drug release of the film was found to be in the range of 89.16±0.16 to 94.82±0.12.

Table 4: *In-vitro* % drug release data of f1 to f9 batches formulations

S. No.	Time (sec.)	% Drug Release data								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	0	0	0	0	0	0	0	0	0	0
2	30	35.65± 0.13	38.14±0.42	31.12±0.09	45.23±0.14	30.56±1.24	37.56±0.12	36.84±0.14	41.43±0.70	38.92±0.06

3	60	48.47± 1.21	55.53±0.46	45.24±0.33	56.27±0.84	41.18±1.34	49.29±0.12	50.93±0.24	52.85±0.07	46.63±0.07
4	90	55.45± 0.23	62.17±0.26	64.56±0.09	69.13±1.36	53.37±0.07	62.31±0.38	62.15±0.45	68.67±0.02	59.23±1.24
5	120	62.23±2.24	71.57±0.09	73.46±1.39	76.34±1.63	62.25±0.07	74.79±2.16	71.91±0.72	79.82±1.53	65.10±1.75
6	150	74.14±2.02	86.69±2.12	84.10±0.63	86.35±0.19	72.54±0.78	82.15±0.70	81.32±0.91	86.27±0.16	76.82±0.02
7	180	89.42±0.33	92.59±0.42	90.14±0.32	90.21±0.35	89.16±0.16	89.36±0.91	91.73±0.53	94.82±0.12	88.53±0.12

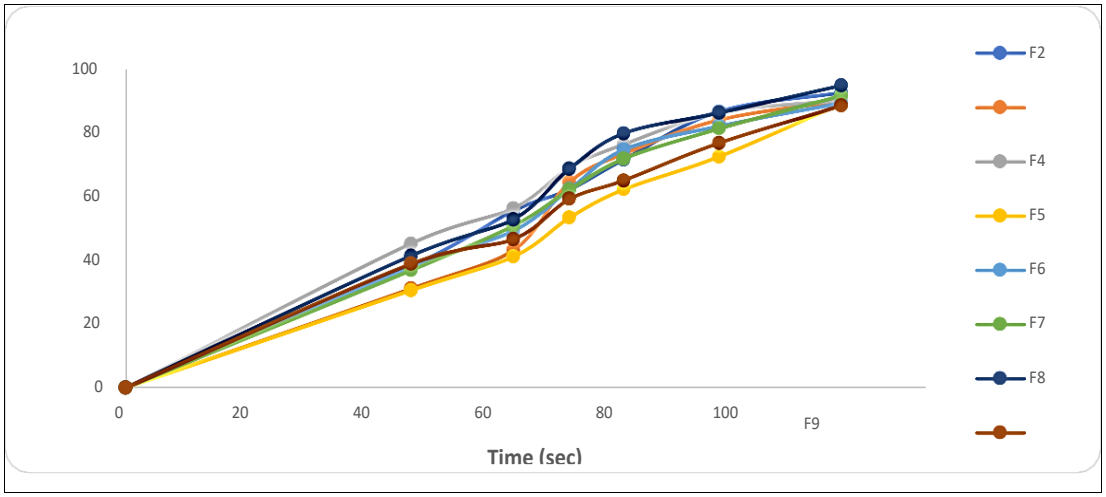

Fig 7: Evaluation of *In-vitro* % *In-vitro* % drug release data of f1 to f9

Conclusion

The fast-dissolving sublingual film of Benidipine Hydrochloride was successfully prepared by the solvent casting method. Benidipine Hydrochloride has poor bioavailability (20-30%), and low aqueous solubility due to first- pass metabolism. The use of Benidipine hydrochloride in the form of the conventional dosage form (tablet) has a poor onset of action and elderly patients have difficulty in swallowing (dysphasia) in solid dosage forms. The fast-dissolving sublingual film of Benidipine Hydrochloride may avoid the first pass metabolism which is the main reason for low bioavailability, provides fast onset of action, and avoid the problem of dysphasia. While the least disintegration time for F8 (29 sec) formulation was observed. Also, the highest dissolution rate was observed for the F8 (94.82 %) formulation. The fast-dissolving sublingual film of Benidipine Hydrochloride provides effective treatment for hypertension.

Conflict of Interest

The authors declare no conflict of interest

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