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Formulation and Evaluation of Fast Dissolving Sublingual Film of Benidipine Hydrochloride for the Treatment of Hypertension

Mayank Sahu, Ankit Anchliya, Bhavana Sahu, Kapil Sahu, Damini Sahu

Abstract: - The sublingual route is very useful for quick onset of action and improved patient compliance. It improves drug utilization and the efficacy of active pharmaceutical ingredients. The oral route is the most preferred by patients. A fast dissolving oral drug delivery system is a solid dosage form that disintegrates or dissolves in the mouth in seconds without the use of water or chewing. The solubility and bioavailability of the drug were enhanced using solid dispersion. The solid dispersion of Benidipine hydrochloride: β-cyclodextrin was prepared in different ratios (1:1, 1:2, 1:3, 1:4) by physical mixture method. The current study discusses the formulation aspects, manufacturing methods such as solvent casting, evaluation parameters, and applications of fast dissolving films by the sublingual route 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. In this study was concluded that the fast dissolving sublingual film of Benidipine Hydrochloride showed a better result as compared to the marketed formulation and all the parameters showed acceptable results.

Introduction

Fast Dissolving Sublingual Films

The term sublingual means under the tongue. It refers to a method of administering drugs by mouth in such a way that the drugs are rapidly absorbed in systemic circulation via a highly vascularized sublingual route in the oral mucosa rather than the digestive tract.

Dysphagia (difficulty swallowing) is a common problem in all age groups, but it is especially difficult for the elderly, children, and patients who are mentally retarded, uncooperative, nauseated, or on low liquid, intake diets to swallow these dosage forms. The drug is administered sublingually, which means it is placed under the tongue and enters the bloodstream directly[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].

The most preferred method for creating a fast-dissolving film is solvent casting methods. An important risk factor for coronary artery disease is hypertension, a common cardiovascular disorder. High blood pressure is referred to as hypertension (HTN) (BP). Systolic blood pressure (SBP) > 140 mmHg and diastolic blood pressure (DBP) > 90 mmHg are the requirements for it to exist[3]. One of the main factors in death from cardiovascular diseases (CVD) like heart failure, coronary heart disease, myocardial infarction, and stroke is hypertension, a globally acknowledged public health issue. According to the World Health Organization (WHO) and the International Society of Hypertension (ISH), hypertension is as common in many developing nations as it is in the developed world, accounting for 4.5% of the global disease burden in 2003[4].

The World Health Organization estimates that nearly 1 billion people in developed and developing nations have hypertension that is below a cutoff of 140/90 mmHg. With 4 million deaths per year and an estimated 1 in 8 deaths caused by the condition worldwide, hypertension is the third leading cause of death[5].

Benidipine Hydrochloride sublingual film can therefore be used to quickly manage hypertension.

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 spectrum of the drug and blend of drug with excipients in the ratio of 1:1 was recorded on the (Shimadzu instrument). The samples were scanned from 4000 to 400 cm-1 by the KBR disc method using an FTIR spectrophotometer. The peaks were compared with the IR tables to define the different functional groups present in the samples[6].

Formulation of Sublingual Film containing Benidipine Hydrochloride: -

The fast dissolving sublingual film of solid dispersion of Benidipine Hydrochloride was prepared by solvent casting technique using HPMC as a film-forming polymer, PEG 400 as a plasticizer, citric acid as a saliva stimulating agent, mannitol as a sweetening agent, and sodium starch glycolate as a super disintegrating agent. The formulation was prepared as per the composition given in the table. The hydrophilic polymer HPMC was accurately weighed and dissolved in distilled water in a beaker and continuously stirred on a magnetic stirrer for 2 hours, PEG 400 was added to the solution and in another beaker sodium starch glycolate, citric acid, and mannitol were dissolved in distilled water and these mixtures were added to the polymeric solution (a solution which contains HPMC and PEG 400). Stirred well using a magnetic stirrer to obtain a homogenous solution and

in the homogenized solution, the accurate amount of the drug (Benidipine Hydrochloride) was added and stirred well for 30 minutes for proper mixing. This solution was allowed to stand for 12 hours for the de-aeration of the solution. The solution was then cast into a petri dish and kept at room temperature for 10 to 12 hours. After drying, films were removed and cut into an area of 2×2 cm2. The sample was stored in a desiccator maintained at a temperature of 30 °±1 °C and relative humidity of 60±5%[7].

Evaluation Parameter of Sublingual Films

The thickness of films:

The thickness of the film was measured with the help of a micrometer screw gauge at three different places the averages of three values were calculated[8].

Weight variation:

The weight variation of the fast dissolving sublingual film of size 2×2cm2 was cut and 3 films of each formulation were taken and weight individually using an electronic balance. The average weight was calculated[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:

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 average of three determinations for each formulation was taken.

% Drug content:

The film (size 2×2 cm2) was cut and placed aside. The volumetric flask was taken and 100ml phosphate buffer pH 6.8 was transferred into that flask and the film was incorporated in that phosphate buffer pH 6.8. The volumetric flask was shaken continuously for 10 min. Then the solution was filtered through Whatman filter paper. After filtration, 1 ml of solution was withdrawn from the above solution in a 10 ml volumetric flask and diluted up to 10 ml with phosphate buffer pH 6.8. The solution was analyzed by UV spectrophotometer at 239.3 nm. To calculate the concentration of drug present in the film[11].

***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 time required for the complete disintegration of the film was noted[12].

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

In-vitro % drug release of fast dissolving sublingual film of Benidipine Hydrochloride was studied 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 5ml sample was withdrawn at specific time intervals and the same quantity was replaced with phosphate buffer pH 6.8 to maintain the volume of the dissolution medium. The sample was filtered immediately through the Whatman filter paper and analyzed using a UV spectrophotometer at 239.3 nm for the determination of drug concentration and calculated the % of drug dissolved or released[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 4: 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

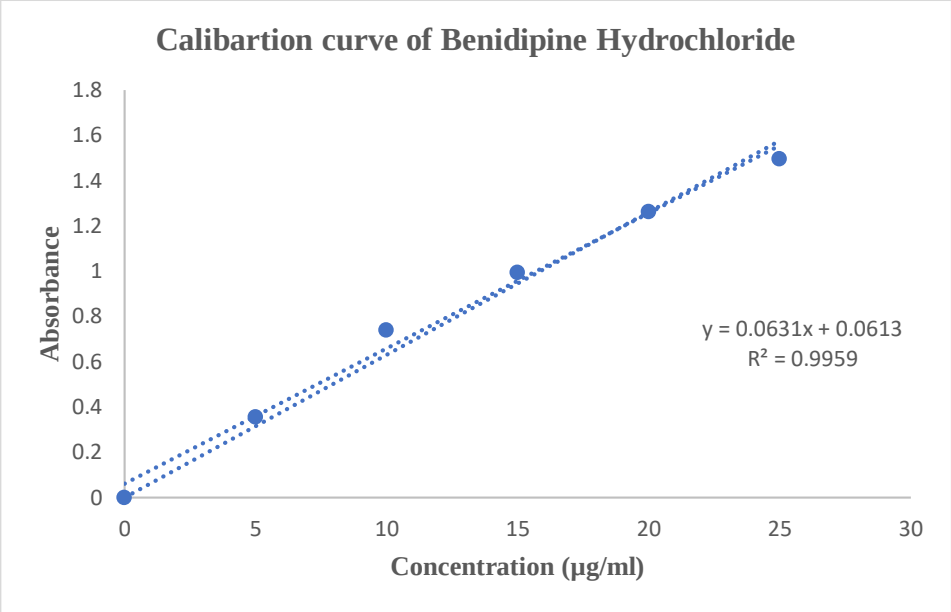

Fig: - Calibration curve in Benidipine Hydrochloride

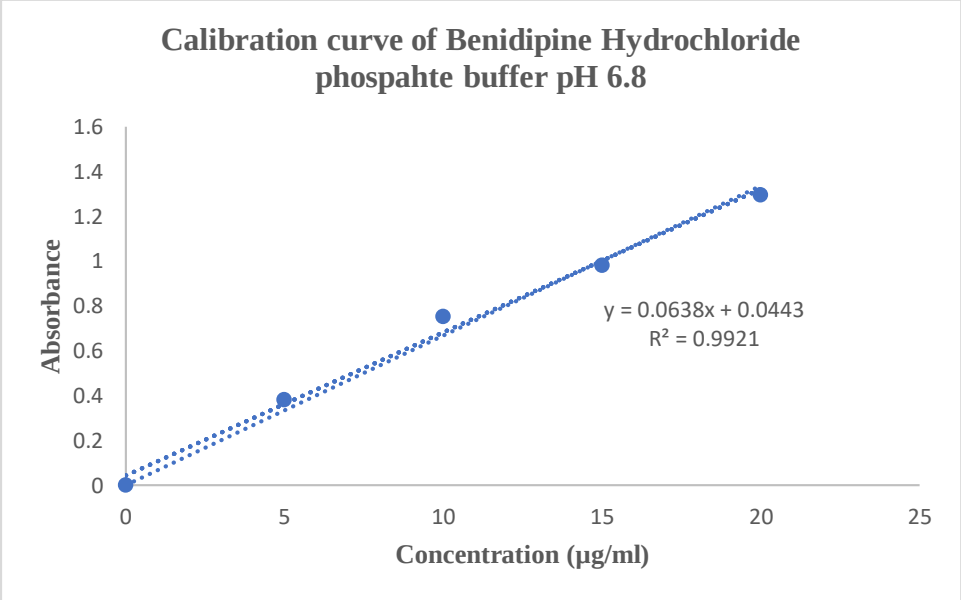

Fig: - Calibration curve in phosphate buffer pH 6.8

- **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.

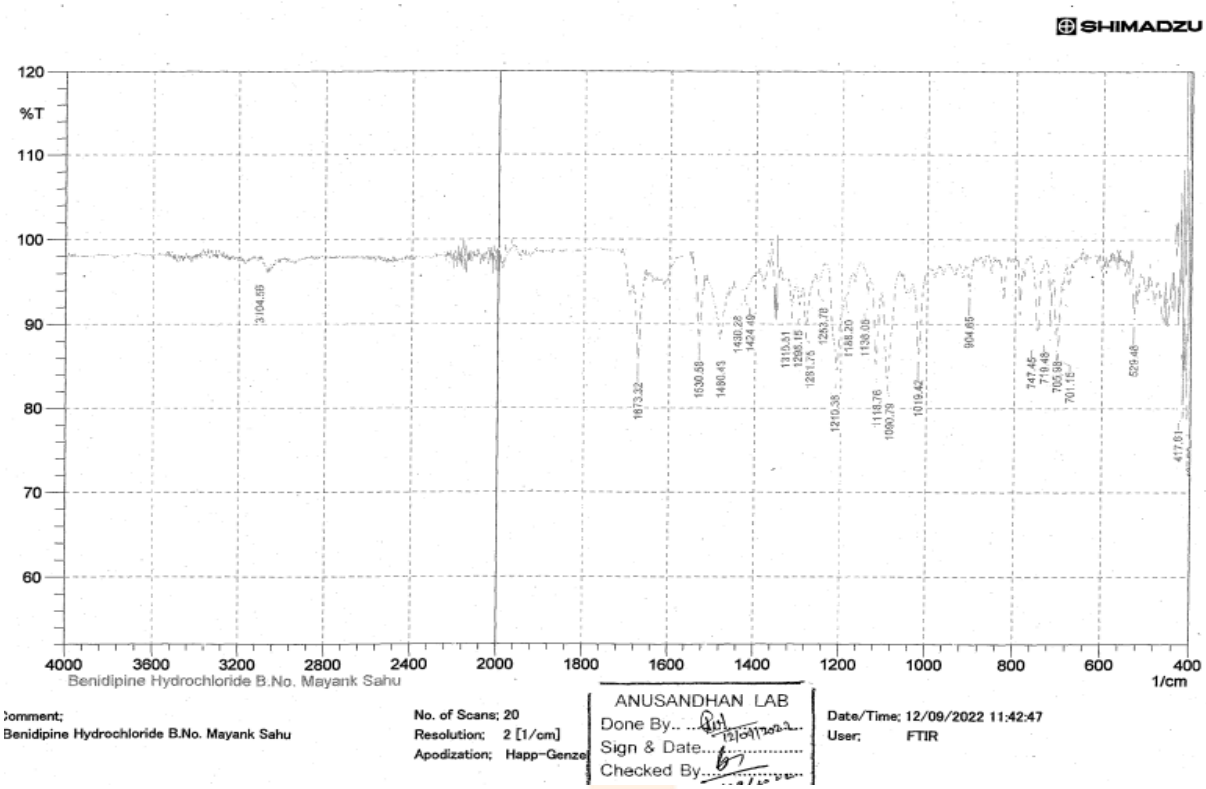

Fig: - FTIR spectrum of Benidipine Hydrochloride

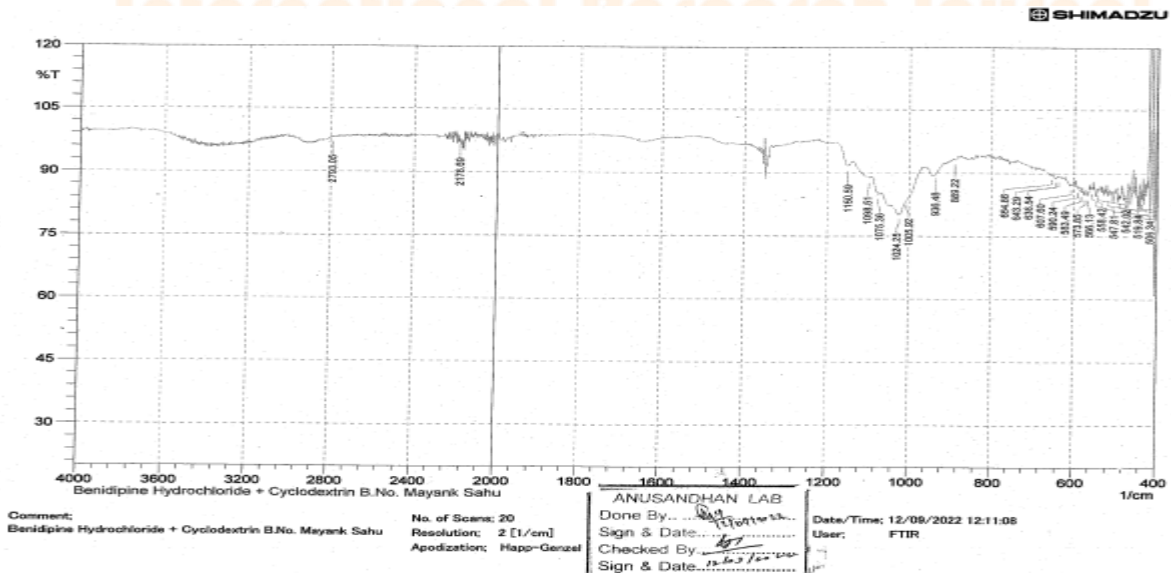

Fig: - FTIR spectra of Benidipine Hydrochloride and β-cyclodextrin solid dispersion

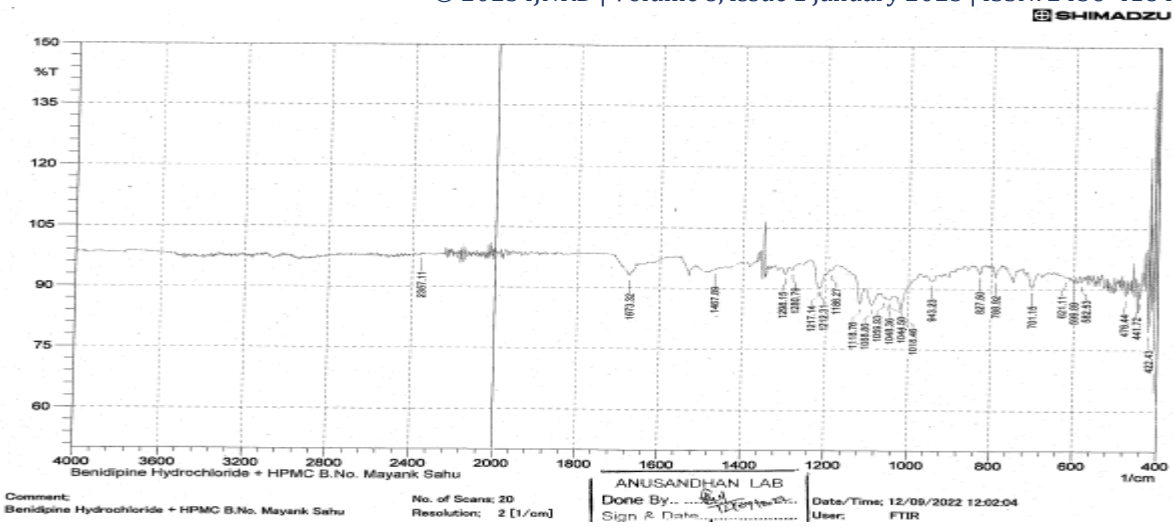

Fig: - FTIR spectrum of physical mixture of Benidipine Hydrochloride and HPMC-E5

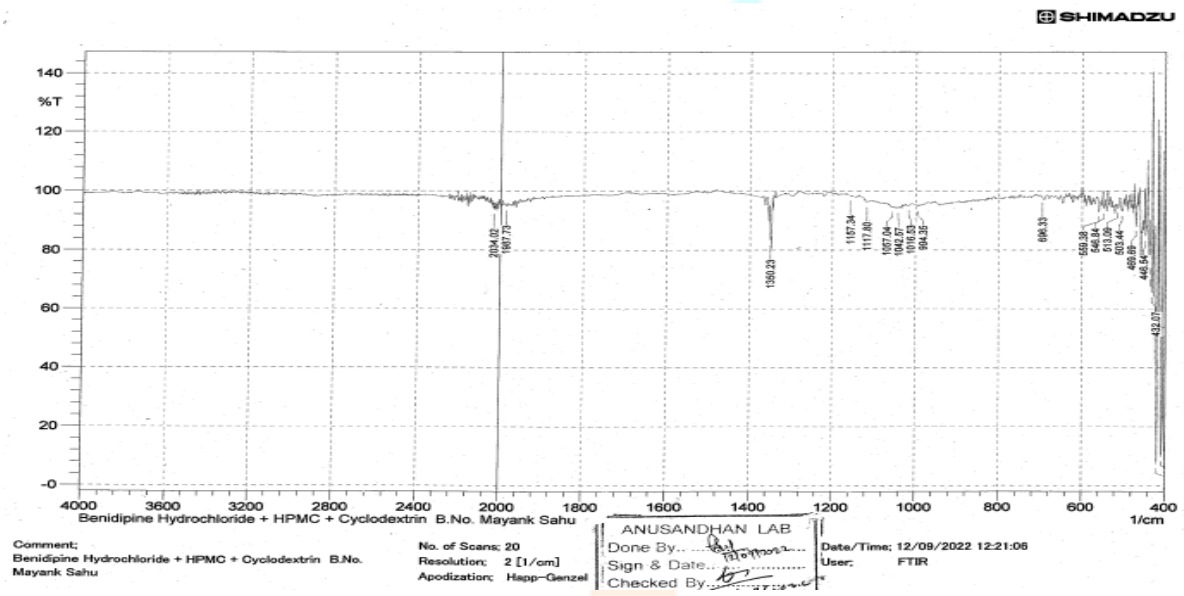

Fig: -FTIR spectrum of HPMC-E5 with Benidipine Hydrochloride and β-cyclodextrin solid dispersion

➢ **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.

- ***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: - 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

Table: - *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

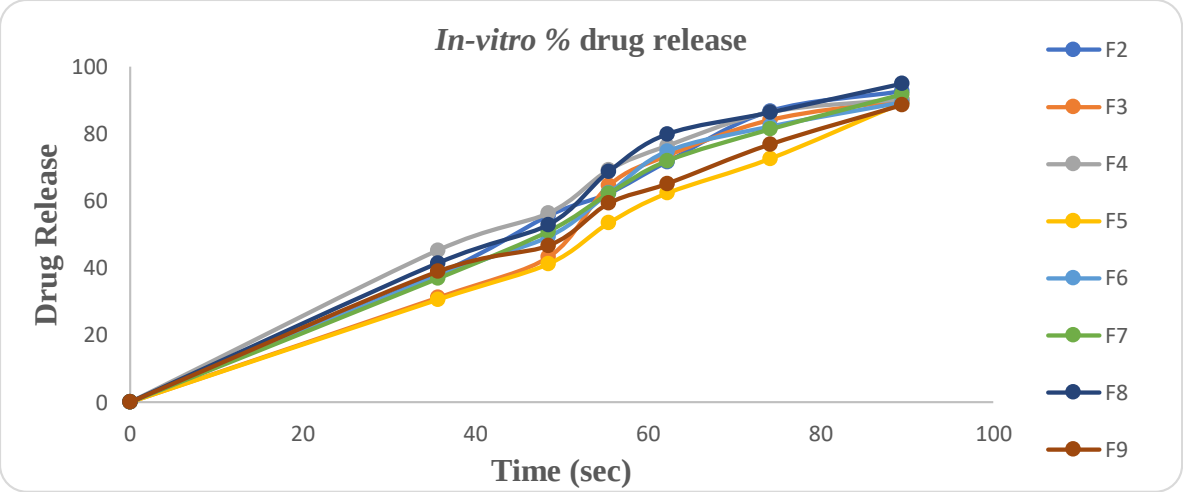

Figure: - Evaluation of *In-vitro* % drug

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.

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