



(RESEARCH ARTICLE)



Formulation and evaluation of mouth dissolving film of antihypertensive agent

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Abstract

Mouth dissolving film is the one of the most advanced oral solid dosage form because of its flexibility and comfort in use. Mouth dissolving films are oral solid dosage form that disintegrate and dissolve within a minute when placed in mouth without taking water or chewing. This dosage form allows the medication to bypass the first pass metabolism so bioavailability of medication may be improved. Mouth dissolving film has potential to improve onset of action lower the dosing and eliminate the fear of choking. Formulation of mouth dissolving films involves both the visual and performance characteristics as plasticized hydrocolloids, API taste masking agents are being laminated by solvent casting and semisolid casting method. Solvent casting method being the most preferred method over other methods because it offers great uniformity of thickness and films prepared having fine glossy look and better physical properties. Mouth dissolving films are evaluated for its various parameters like thickness, physical property like folding endurance, disintegration and dissolution time. This review gives an idea about formulation techniques, evaluation parameters, overview on packaging and some available marketed products of mouth dissolving films.

Keywords: Mouth Dissolving Film; Technology; Thickness; Fast relief

1. Introduction

1.1. Oral Dosage form

The oral route of administration still continue to be the most preferred route due to its manifold advantages including ease of ingestion, pain avoidance, versatility and most importantly patient compliance. The most popular dosage forms are tablets and capsules. In last two decades, due to enhanced demand of patient compliance a vast research took place in this area. There are around 350 drug delivery systems developed in accordance with patient compliance.

Geriatric patients may have difficulty in swallowing and chewing the tablets resulting in patient noncompliance and ineffective therapy. To overcome these problems mouth dissolving tablets are a very good option. They disintegrate and get dissolved faster in saliva without the usage of water. As a result it explains good patient compliance [1].

The demand for this fast and mouth dissolving technology was approximately 16.50 billion US dollars in the year 1996 but now it is expected to grow about 80 billion U S dollars every year.

To overcome such problems in geriatric patients a newer dosage form has been introduced which is regarded as mouth dissolving tablets or films. It is one of the novel approaches which involves rapid disintegration or dissolution of dosage form inside the mouth without the need for water.

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A dosage form of a drug is a formulation suited for administration to the patient by various routes for diagnosis or treatment of disease. Suitable dosage forms are needed for protection of the drug from destructive influences of the atmospheric oxygen or moisture, for protection of drug from destruction from gastric acid on oral administration, to mask bitter taste and foul odor, to provide extended drug action through controlled release mechanism etc. Following agents are used with the drug in the suitable dosage form [2].

Fast dissolving films are the most advanced form of oral dosage form because of its flexibility and comfort. It provides increased efficacy of active pharmaceutical ingredients by getting dissolved within minutes in oral cavity. This type of technology is very useful in case of pediatric, geriatric, bedridden and unconscious patients. [3]

There is no need of water administration and this dosage form gives quick absorption and provides high permeability of around 4-1000 times in oral mucosa. [3]

2. Material and method

2.1. Preformulation Studies

2.1.1. Melting Point

The melting point of drug Perindopril was determined with the help of melting point apparatus. In this method drug was poured in capillary tube with one end closed. Insert the capillary tube in melting apparatus. Start the apparatus and wait till the drug melts. Record the temperature at which drug melt.

2.1.2. Solubility

Solubility of Perindopril was determined in different solvents like water, methanol, ethanol, and chloroform and PBS pH 6.8

2.1.3. Standard curve of Perindopril in PBS pH 6.8

Procedure

- Preparation of PBS pH 6.8

28.8 g of sodium dihydrogen phosphate, 11.45 g of potassium dihydrogen phosphate was dissolved in 1000 ml of distilled water.

- Preparation of standard stock solution

100 mg of Perindopril was accurately weighed with the help of weighing balance and poured in to 100 ml volumetric flask. Drug was dissolved in 100 ml phosphate buffer pH 6.8 and volume was made up to 100 ml in volumetric flask.

2.1.4. Procedure for plotting calibration curve of pure drug

From the standard solution of perindopril was subsequently diluted with water to obtain a series of dilutions containing 20-100 µg/ml of perindopril in 1 ml solution. The absorbance of these solutions was measured at 221 nm UV spectrophotometer against corresponding blank. The concentration of perindopril and the corresponding absorbance values are given in table. The calibration curves for the estimation of perindopril were constructed by plotting linear best fit between concentration of Perindopril and corresponding mean absorbance value are shown in figure.

2.1.5. Drug excipient interaction study by FT-IR

Interaction of perindopril with all the polymers like xanthan gum and maltodextrin was observed with the help of FT-IR technique. The spectrum of drug is taken with the help of KBr pellet technique. Pellets of drug and KBr were prepared using hydraulic press and analyzed in FT-IR spectrophotometer.

2.2. Formulation of drug loaded mouth dissolving film

- Mouth dissolving film of perindopril was prepared with the help of solvent casting method.
- Xanthum gum and maltodextrin were dissolved in 7 ml of distilled water.
- This mixture was kept still for some time and then drug is added by continuous stirring.

- All the other ingredients were added by one by one until a proper polymer solution is obtained.
- The flavoring agent and coloring agent were added at the end in above polymeric solution by continuous stirring.
- The prepared mixture was kept aside for some time for removal of air and then it is placed on glass slide.
- The film was dried for about 12 hrs.
- After proper drying film was removed from slide and cut into desired sizes.

Table 1 Formulation of Mouth dissolving film batches

Sr. No	Ingredient	F1	F2	F3	F4	F5	F6
1	Drug	20	20	20	20	20	20
2	Xanthum Gum(mg)	100	150	200	-	-	-
3	Maltodextrin (mg)	-	-	-	100	150	200
4	PEG 400 (ml)	0.4	0.4	0.4	0.4	0.4	0.4
5	Sodium Starch Glycolate (mg)	10	10	10	10	10	10
6	Citric acid (mg)	5	5	5	5	5	5
7	Sucrose (mg)	5	5	5	5	5	5
8	Vanillin (mg)	5	5	5	5	5	5
9	Amaranth (mg)	q.s	q.s	q.s	q.s	q.s	q.s
10	Water (ml)	8	8	8	8	8	8

2.2.1. Evaluation of mouth dissolving film

The mouth dissolving films of perindopril were evaluated with the help of different parameters

- Physical appearance
- Surface texture
- Morphology of film
- Weight uniformity
- Thickness
- Surface pH
- Folding endurance of film
- *In vitro* disintegration time
- *In vitro* drug release

Physical appearance

The physical appearance of mouth dissolving film of perindopril was observed by visual inspection.

Surface Texture

The surface evaluation of mouth dissolving film was observed by feel and touch of film.

Morphology of film

Perindopril films were observed for surface morphology with the help of SEM (Model no JSM 6390A Japan). The sample was mounted on slab it is coated with gold (2nm) under reduced pressure using an ion sputtering device. The gold coated films were analyzed for surface topography and photographs of desired magnification were obtained.

Weight Variation

The films of different formulation of size 2x2 cm were weighed individually using digital balance and average weight was calculated.

Thickness of film

The thickness of mouth dissolving film of perindopril was measured with the help of screw gauge having a least count of 0.01mm. The thickness was measured at three different spots and average of thickness was calculated.

Surface pH of film

It was determined by allowing contact of surface of film with 1 ml of distilled water. After sometime, surface pH of film was obtained by dipping pH paper in the solution for around 1 minute.

Folding endurance of film

The term folding endurance means flexibility of film. In this method 2x2 cm piece of film is taken. It is folded at same place many times till the film gets broke. The number of times a film can be folded gives the approximate value of folding endurance.

In vitro disintegration time

In this method take a piece of film (2x2 cm). place it on a glass petri dish containing 10 ml of distilled water. The time required for film to break the first particle of film was noted down which is considered as *In vitro* disintegration time. This procedure is repeated for 3 times.

In vitro drug release studies

In this method take a piece of film (2x2 cm). It was placed in a stainless steel wire mesh with sieve opening of 700 μm . The mesh is placed in dissolution media (PBS pH 6.8) around 300 ml. The dissolution process is carried out by 6 stage paddle apparatus at 37 °C at 50rpm. 5ml of sample is withdrawn at time intervals 0,1,2,3,4,5,10,15 and 30 minutes. After withdrawing sample a fresh 5ml blank is added to the apparatus to maintain the sink condition.

3. Results

3.1. Melting Point

Melting point of perindopril was found to be 124 °C to 126 °C.

3.2. Solubility

The drug perindopril was found to be freely soluble in distilled water, alcohol and phosphate buffer (pH 6.8).

3.3. UV estimation of perindopril in phosphate buffer pH6.8.

Perindopril was estimated in pH 6.8 at 210 nm.

Table 2 UV estimation of perindopril in phosphate buffer pH 6.8

S.No	Concentration	Absorbance
1	20	0.2040±0.0040
2	40	0.4030±0.0022
3	60	0.6220±0.0020
4	80	0.7820±0.0024
5	100	1.0101±0.0050

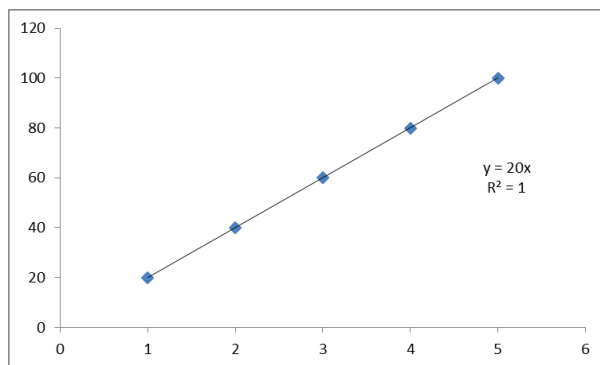


Figure 1 UV estimation of perindopril in phosphate buffer pH6.8

3.4. Drug Excipient compatibility Studies

The IR spectra of pure drug with polymer like Xanthum Gum and Maltodextrin are observed with the help of FT-IR.

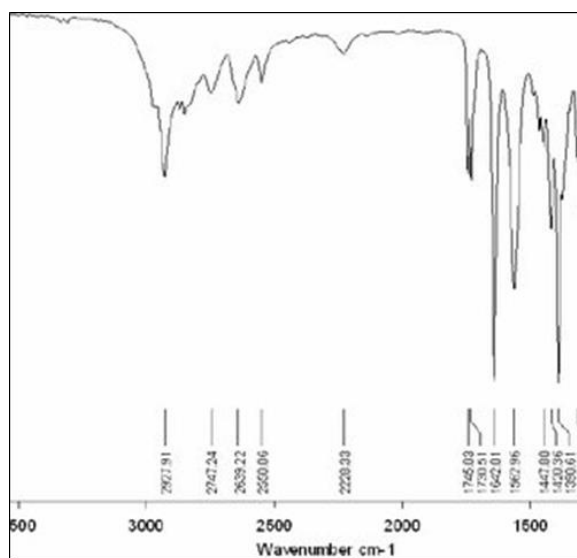


Figure 2 FT-IR spectra of Perindopril

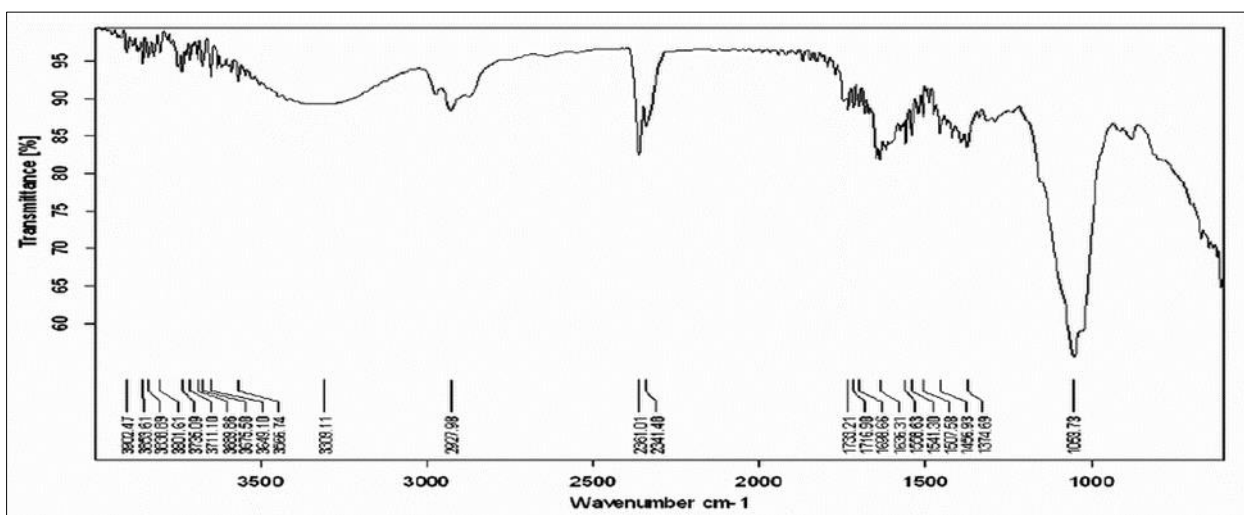


Figure 3 FT-IR spectra of Perindopril and Xanthum Gum

3.5. Differential Scanning Colorimetry

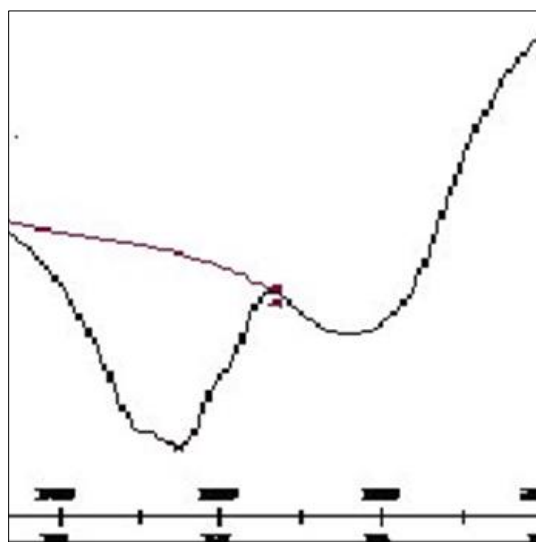


Figure 4 DCS of Perindopril

3.6. Evaluation of mouth dissolving film of perindopril

3.6.1. Physical Appearance:

It was checked by visual inspection and it was found that the film was attractive and elegant in nature. It was uniformly prepared.

3.6.2. Surface Texture

The surface texture of film was found to be smooth and soft in nature.

3.7. Surface morphology of film

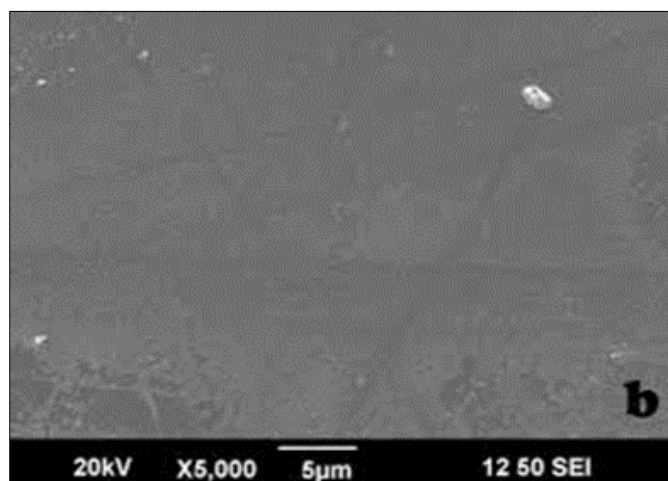


Figure 5 SEM of mouth Dissolving film of perindopril

3.7.1. Weight Variation

The weight of prepared film was determined with the help of digital balance.

Table 3 Weight variation parameter

S. No	Average Weight
F1	34.30±0.50
F2	33.32±0.56
F3	36.35±0.48
F4	19.20±0.57
F5	27.60±0.62
F6	41.00±0.50

3.7.2. Thickness

The thickness of mouth dissolving film was found to be

Table 4 Thickness of different batches of film

S. No	Thickness
F1	95.00±0.50
F2	100.0±0.56
F3	102±0.48
F4	101±0.57
F5	97.2±0.62
F6	99.8±0.50

3.8. Folding Endurance

Table 5 Folding Endurance of film

S. No	Folding Endurance
F1	280±3.000
F2	281±2.565
F3	275±3.005
F4	280±2.645
F5	283±3.000
F6	280±3.063

3.9. Surface pH

Table 6 Surface pH of film

S. No	Surface pH
F1	6.65±0.152
F2	6.72±0.172
F3	6.63±0.173
F4	6.56±0.057
F5	6.81±0.129
F6	6.53±0.321

3.10. *In vitro* disintegration Time

Table 7 *In vitro* disintegration Time of film

S. No	Disintegration Time
F1	45.0±0.441
F2	48.6±0.415
F3	32.6±0.895
F4	26.56±0.457
F5	38.4±0.500
F6	36.53±0.897

3.11. *In vitro* Drug Release

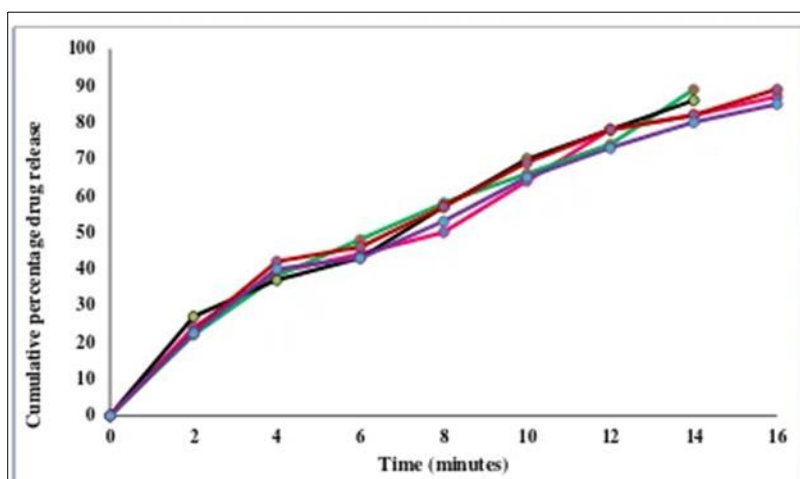


Figure 6 *In vitro* drug release

4. Discussion

Perindopril is a hypertension drug. Hypertension is one of the primary risk factors for cardiovascular diseases, including cardiovascular stroke. The absolute bioavailability of perindopril is approximately 60-75%. Following absorption, perindopril is hydrolyzed to Perindoprilat, which has an average bioavailability of 20%. However, food decreases the extent of biotransformation to Perindoprilat and reduces its bioavailability by 35%. To overcome the above mentioned problems an attempt was made to develop and to improve the solubility of drug and reduce side effects, it was attempted to develop fast dissolving films with some natural polymer.

FTIR spectroscopic studies were carried out in order to establish compatibility between drug and excipients. The results were concluded that there were no chemical interactions between drug and the excipients used, so they could be used for the formulation of perindopril fast dissolving films.

DSC studies were carried out for optimized formulation a sharp exothermic peak observed at 127 °C corresponding to its melting point of the drug. The results were concluded that there were no chemical interactions between drug and the carriers used.

Around six formulations of perindopril were developed as fast dissolving films using various excipients which were found to be compatible using FTIR of films. Formulation F1-F6 was perindopril fast dissolving films prepared using different polymers such as, Xanthan gum and maltodextrin.

Perindopril films were evaluated for quality control tests such as thickness, weight variation, folding endurance, SEM, surface pH, disintegration time, *in-vitro* diffusion, drug content, kinetic studies and stability study.

5. Conclusion

- Perindopril fast dissolving films have been successfully prepared by solvent casting method.
- Perindopril is an anti-hypertension drug was selected for the preparation of fast dissolving films.
- Xanthan gum, was used as polymer for the preparation of perindopril mouth dissolving films.
- Perindopril films were prepared by solvent casting method using Xanthan gum, maltodextrin at 100,150,200 mg respectively. Based on this physicochemical characterization *In vitro* drug diffusion and drug release kinetics of perindopril showed 93.5% of drug at the end of 16th min.
- The evaluation test for films of perindopril suggest that it is promising to be developed as fast dissolving films with above mentioned excipients which can enhance the diffusion, thereby the release and hence the bioavailability may be effected and may have impact on its bioavailability.

Compliance with ethical standards

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Disclosure of conflict of interest

No authors have conflict in publishing this article report.

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