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Research Article

## Formulation and Evaluation of Buccoadhesive Tablet of Verapamil Hydrochloride for the Treatment of Hypertension

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### Abstract

The creation and assessment of buccoadhesive tablets of verapamil hydrochloride were the study's primary goals. Blood pushing excessively hard against the arterial wall is referred to as hypertension. Typically, hypertension is characterized by blood pressure readings over 140/90; readings over 180/120 are regarded as severe hypertension. Verapamil is used to manage angina (chest pain) and treat excessive blood pressure. Verapamil belongs to the category of drugs known as calcium channel blockers. In order to save the heart from having to pump as hard, it relaxes the blood artery. Additionally, it enhances the heart's blood and oxygen flow while decreasing electrical activity to regulate heart rate. Five formulations that demonstrated satisfactory physicochemical characteristics and drug release were chosen for the investigation. Physical examination, weight fluctuation, uniformity of content, thickness, friability, hardness, and in vitro drug release were used to characterize the formulation. In terms of physical examination, weight variation, uniformity of content, thickness, friability, hardness, and in vitro drug release, all formulations produce satisfactory results. The buccoadhesive tablet formulation (F2 Batch) had the best in vitro drug release of 87% in 8 hours. Verapamil hydrochloride's UV spectrum was examined, and it was discovered that the drug's highest absorbance occurs at 227nm, increasing its bioavailability.

**Keywords:** Verapamil Hydrochloride, Hypertension, Bioavailability, Buccoadhesive Tablet, Calcium channel blocker.

## 1 INTRODUCTION

Significant interest has been exhibited recently in the creation of innovative bioadhesive dosage forms for mucosal administration of medications that aim to get around these restrictions. Materials that adhere to biological substrate, such as mucosal membranes, are referred to as "bioadhesives." Adhesion of bioadhesive drug delivery devices to mucosal membranes increases the gradient of drug concentration at the site of absorption, improving the bioavailability of a drug that is administered systemically. Additionally, bioadhesive dose forms have been utilised to address local disorders at the mucosal surface (such as mouth ulcers) in an effort to reduce total dosage requirements and minimise potential side effects from systemic drug administration. Passive diffusion into the lipoidal membrane is the principal route by which drugs are absorbed into the oral mucosa<sup>1</sup>.

The lamina propria, an underlying layer of connective tissue, and a stratified squamous epithelium that may or may not be keratinized make up the oral mucosa, the mucous membrane that lines the mouth cavity. Mucus is produced by the major and innumerable minor salivary glands and helps to keep the skin wet. Unique sensory endings for taste are located on the tongue's dorsal surface, and the oral mucosa is densely covered in nerve endings. A diverse submucosa covers the lamina propria of the oral cavity. The lamina propria and submucosa may resemble each other structurally enough to gradually merge<sup>2</sup>.

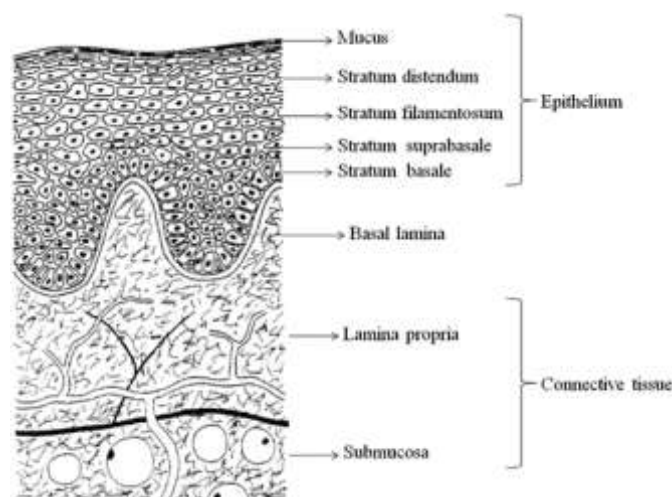
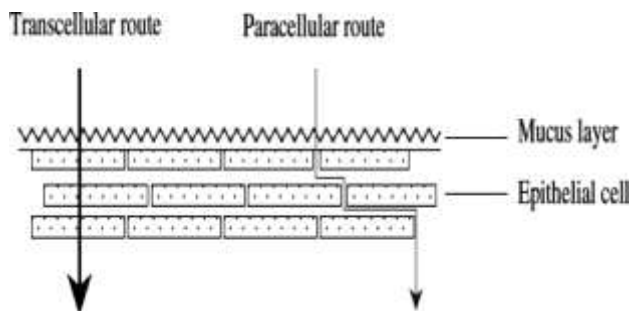


Figure 1: Cross Section of buccal mucosa<sup>3</sup>

Drug Transmembrane Permeability:<sup>4</sup>

The squamous stratified epithelium of the oral mucosa can absorb drugs in one of two ways:

1. Transcellular (intracellular; moving within a cell).
2. Intercellular (paracellular; around the cell).



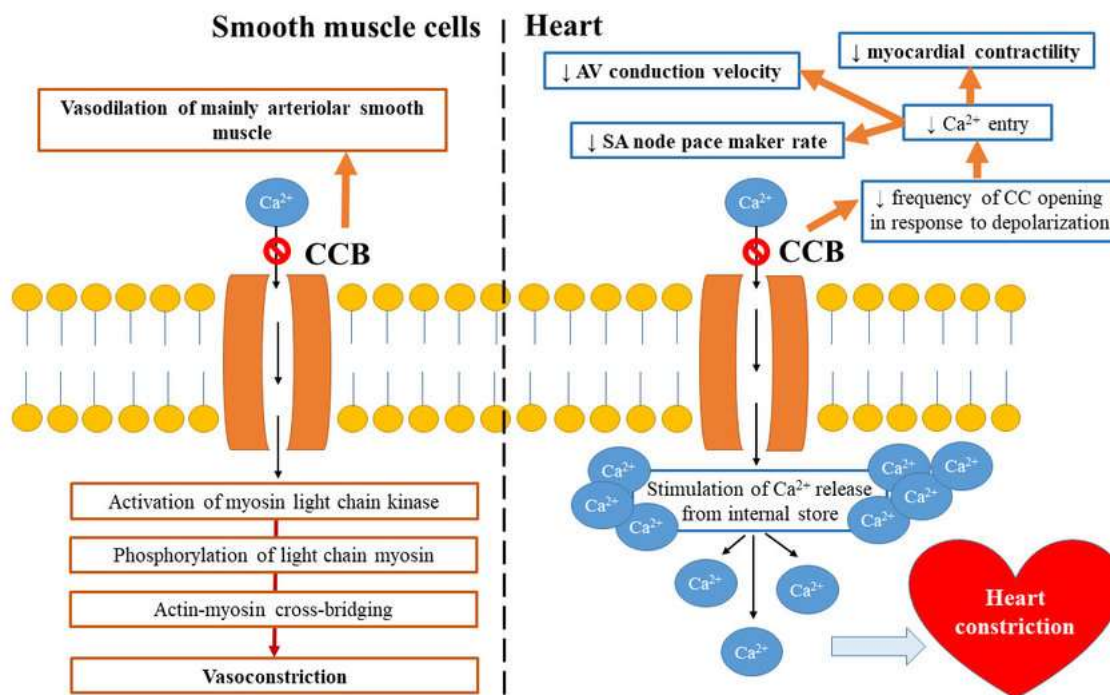
**Figure 2: Drug Transmembrane Permeability through Buccal Mucosa<sup>5</sup>**

A chronic medical disease known as hypertension or high blood pressure causes raised blood pressure in the arteries. Either primary (essential) or secondary classifications apply to it. "Primary hypertension" refers to high blood pressure without a known medical reason and accounts for about 90–95% of cases. Secondary hypertension, which affects the remaining 5–10% of patients, is brought on by various illnesses that affect the kidneys, arteries, heart, or endocrine system. Chronic hypertension is a major contributor to chronic kidney failure and one of the risk factors for stroke, heart attack, heart failure, and arterial aneurysm. Life expectancy is decreased when arterial blood pressure is moderately elevated. Medication, dietary and lifestyle modifications, and a reduction in the risk of associated health issues can all help regulate blood pressure<sup>6</sup>

Verapamil hydrochloride, a phenyl alkylamine calcium-channel blocker and class IV antiarrhythmic, is a medication that is frequently used to treat hypertension, ischemic heart disease, such as angina pectoris, myocardial infarction, and arrhythmias. Presystemic hepatic metabolism of verapamil causes up to 80% of the dosage to be excreted in this manner. Thus, 20–30% of the bioavailability is achieved.<sup>2</sup> Since this medication is rapidly removed and has a short elimination half-life of 2–7 hours, daily dosage is necessary to maintain effective plasma levels.

Verapamil may be absorbed more effectively from the buccal mucosa than the digestive tract<sup>4,5</sup>. A sizable portion of the buccal mucosa, which is non-keratinized, heavily blood-supplied, and has a dense capillary artery network, is used for medication absorption. Drugs can thus circumvent the first-pass metabolism in the intestine and liver or evade inactivation in the stomach and enter the systemic circulation straight through capillary capillaries.<sup>6</sup> Because of this, the medicine has higher bioavailability parameters upon administration of a lower dose than in normal tablets.

As a result, there is particular interest in this study for the development of bucoadhesive tablets because Vp-HCl is a suitable candidate for administration via a buccal delivery system that provides controlled drug delivery without pre-systemic metabolism due to its short half life and extensive first pass metabolism.<sup>7</sup>



**Figure 3: Mechanism of calcium channel blocker (CCB) Action<sup>8</sup>**

**Benefits of the buccal medication delivery technique include:<sup>9</sup>**

- The drug is simple to administer, and stopping medication in an emergency may be made easier.
- A lengthy period of drug release.
- Drugs can be given to unconscious and injured patients.

Due to its ability to bypass first pass metabolism, the drug has a high bioavailability.

- Drugs that are unstable in the acidic environment of the stomach can still be delivered orally.

Passive diffusion is the process used in drug absorption.

- The high rate of absorption is caused by tight contact with the absorbing membrane surface.

- Quick start of action.

#### Drug distribution with buccoadhesive restrictions:

- It is not possible to deliver medications that are unstable at buccal pH.
- Drugs that have an acrid, bitter taste, sickening scent, or cause irritation cannot be administered using this route.
- Only this approach can be used to administer drugs in modest doses or quantities.
- This approach can be used to provide medications that must only be absorbed by passive diffusion.

## 2 AIM AND OBJECTIVE

Aim: Creation and assessment of buccoadhesive verapamil hydrochloride tablets.

Objective:

1. Developing patient-compliant dose forms is preferable than traditional ones.
2. To increase the drug's bioavailability, safety, and effectiveness
3. To create and produce the most effective and trustworthy dosage form
4. To evaluate and choose an appropriate polymer for buccal medication delivery

## 3. IMPORTANCE OF RESEARCH

1. A brand-new oral mucosal drug delivery technology is the buccoadhesive tablet.
2. They can overcome every drawback of the standard dosage forms that are currently available.
3. It does not go through first pass metabolism.
4. It has better bioavailability.

## 4. MATERIAL AND EQUIPMENT USED

**Table 1: List of Material Used**

Sr No	Materials	Source
1	Verapamil hydrochloride	Obained as gift sample
2	Carbopol-934	SD. Fine chemical Ltd Mumbai
3	HPMC K-4	SD. Fine chemical Ltd Mumbai
4	HEC	SD. Fine chemical Ltd Mumbai
5	Na-CMC	SD. Fine chemical Ltd Mumbai
6	Aspartame	SD. Fine chemical Ltd Mumbai
7	Talc	SD. Fine chemical Ltd Mumbai

**Table 2: List of Equipment Used**

Sr No	Equipment	Source
1	Electronic weighing balance	Contech Instruments Ltd Navi Mumbai
2	Digital Thickness Tester	Linker, Mumbai
3	Monsanto Hardness tester	Praveen Enterprises, Bangalore
4	Friability Test Apparatus	Indian Equipment Corporation
5	PH Meter	MC Dalai, Chennai
6	Digital Tablet Dissolution Test Apparatus	Disco 2000Lab India,Mumbai
7	UV-1800 spectrophotometer single beam	Shimadzu UV-Spectrophotometer
8	FTIR	Shimadzu Japan

## 5. METHODOLOGY

### 5.1. Requirements: -

#### Apparatus: -

Mortar and Pestle, Measuring Cylinder, Spatula, Pipette

#### Equipment: -

Calibrated weighing balance, Tablet Punching machine

#### Chemicals: -

Carbopol-934, HPMC-K4M, HEC, Na-CMC, Aspartane, Talc

### 5.2. Method of Preparation: -

**5.2.1** By adopting a direct compression approach and varying concentrations of carbopol 934 P, HPMC K15M, hydroxy ethyl cellulose, and Na CMC, buccoadhesive tablets containing verapamil hydrochloride were created. All ingredients with the exception of talc were uniformly combined. Talc was added and thoroughly mixed for an additional two to three minutes after the medication and other components had been sufficiently combined, and then the tablet was compacted with a 9mm punch.

### 5.2.2. Preformulation Study<sup>1</sup>

#### Evaluation of Verapamil Hydrochloride

**1. Organoleptic parameters of the drug:** The drug's physical attributes, colour, taste, aroma, and other attributes were assessed.

**2. Determination of Solubility:** Use an ever-more-rigorous mechanical technique to dissolve all the compounds in various solvents.

**3. Determination of melting point:** Verapamil Hydrochloride's melting point was discovered to be between 131 and 133°C, which complied with IP criteria and indicated purity of the chosen medication sample.

**4. Determination of Lambda max**

For the calibration curve's preparation, methanol was used. To obtain a concentration of 1000 ppm, 100 mg of verapamil hydrochloride were dissolved in distilled water and diluted up to 100 ml, which is referred to as a stock solution. To achieve various concentrations, this stock solution underwent further dilution. Using a UV spectrophotometer, the resulting solutions were checked for max in the 200–400 nm wavelength range.

#### 5. Interpretation of the IR spectrum

The distinctive functional groups in the extract were located using Fourier transform infrared (FTIR). The drug was dissolved in dry potassium bromide (KBr) in a tiny quantity (5 mg). The mixture was well combined in a mortar before being compressed at 6 bars for 2 minutes to create a thin disc of KBr. Next, a sample cup of a diffuse reflectance accessory was used to hold the disc. From 4000 to 400 cm<sup>-1</sup>, the sample was scanned.

### 5.2.3. Formulation of buccoadhesive tablet

**Table 3: Formulation of buccoadhesive tablet**

Sr no.	Ingredients	F1	F2	F3	F4	F5
1	Verapamil HCL	50mg	50mg	50mg	50mg	50 mg
2	Carbopol-934	75mg	60mg	75mg	60mg	75mg
3	HPMC-K4M	65mg	80mg	-	-	-
4	HEC	-	-	65mg	80mg	-
5	Na-CMC	-	-	-	-	65mg
6	Aspartane	6mg	6mg	6mg	6mg	6mg
7	Talc	4mg	4mg	4mg	4mg	4mg

HPMC : Hydroxy propyl methyl cellulose, HEC : Hydroxy Ehtyl Cellulose , Na-CMC : Sodium carboxy Methyl cellulose

All the quantities are in mg.

Total weight of one tablet is 200 mg All the quantities are in mg.

### 5.2.4. Preparation of Buccoadhesive tablet

By adopting a direct compression approach and varying concentrations of carbopol 934 P, HPMC K15M, hydroxy ethyl cellulose, and Na CMC, buccoadhesive tablets containing verapamil hydrochloride were created. All ingredients with the

exception of talc were uniformly combined. Talc was added and thoroughly mixed for an additional two to three minutes after the medication and other components had been sufficiently combined, and then the tablet was compacted with a 9mm punch.



**Figure 4: Prepared buccoadhesive tablet of verapamil hydrochloride**

### 5.3 Evaluation Parameter of Buccoadhesive tablet

#### 5.3.1 Physical Appearance:

All the batches were visually evaluated for physical appearance, colour, odour, and taste.

#### 5.3.2 Weight Variation:

20 tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of 20 tablets were calculated. The batch passes the test for weight variation test if not more than two of the individual tablet weight deviate from the average weight by more than the percentage shown in Table No.4.

**Table 4: Percentage deviation allowed under weight variation test**

Average weight of tablet (mg)	Percentage deviation
130 or less	10
130-324	7.5
More than 324	5

#### 5.3.3 Uniformity of content

weigh and mix Using 20 tablets, precisely weigh 100 mg of verapamil hydrochloride in powder form. Shake 150 ml of phosphate buffer pH 6.8 for 10 minutes. Add enough phosphate buffer pH 6.8 to make 200 ml. Filter. 10ml of filtrate should be diluted to 100ml of water, and the highest absorbance of the resultant solution should be measured at 227nm. The outcomes are displayed in table no. 9.

#### 5.3.4 Thickness

Three tablets were selected randomly from each batch and thickness was measured by using vernical calipers. The results are shown in table no 9.

#### 5.3.5 Friability

Five tablets were weighed and placed in the Roche friabilator and apparatus was rotated at 25 rpm for 4 minutes. After revolutions the tablets were dusted and weighed again. The percentage friability was measured using the formula.  $\% F = \{1 - (W/W_0)\} \times 100$  Where, % F = friability in percentage  $W_0$  = Initial weight of tablet  $W$  = weight of tablets after revolution The results are shown in table no 9.

#### 5.3.6 Hardness

Hardness was measured using Monsanto hardness tester. For each batch two tablets were tested. The results are shown in table no 9.

#### 5.3.7 Buccoadhesive strength

In order to provide a decent adhesiveness without any issues, the buccoadhesive property of verapamil hydrochloride tablets containing varied proportions of polymers was determined. The kind and concentration of the buccoadhesive polymers had an impact on the buccoadhesion characteristics. The F2 formulation, which contains Carbopol 934 P and Na CMC, was proposed to have the highest adhesion force, or maximum detachment force (25.1 gm).

#### 5.3.8 In vitro release study

All the formulations of prepared buccoadhesive tablets of verapamil hydrochloride subjected to in vitro release studies these studies were carried out using dissolution media of

phosphate buffer 6.8 pH. Medium used for release rate study was 900 ml phosphate buffer pH 6.8 during the course of study whole assembly was maintained at  $37 \pm 0.5$ . withdraw a 5ml of sample at time interval of 1,2,3,4,-upto 8hrs and replaced with 5ml of fresh dissolution medium. The withdrawn samples were dikute with dissolution medium and then filter it with whattman filter paper and assayed at 278nm. The release of verapamil hydrochloride from buccoadhesive tablet varied according to the type and concentration of the polymer. The % release of Batch F1,F2,F3,F4,F5 was found to be 83%,87%,79%,75% 73% resp. in 8 hrs.

## 6. RESULT AND DISCUSSION

### 6.1. Pre-formulation Study

#### 6.1.1. Organoleptic Parameter

**Table 5:**

Parameters	State
Colour	White
Taste	Bitter
Odour	Characteristic
State	Solid

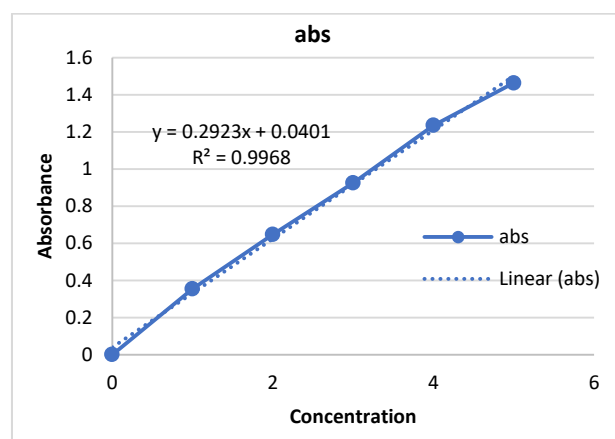
#### 6.1.2. Determination of Solubility

**Table 6:**

Solvent	solubility behaviour
Water	Soluble
Acetone	Insoluble
Ethanol	Soluble
Methanol	Soluble
Chloroform	Soluble

#### 6.1.3. Determination of Lambda max

After studying the UV- spectra of ginger rhizome extract, it was found that it shows maximum absorbance at 227nm. So, absorbance at 278 nm was considered as  $\lambda_{max}$  for Verapamil Hydrochloride.



**Figure 5: UV Spectra of Verapamil HCL**

### 6.1.4. Interpretation of IR spectrum

The identity of drug was confirmed by comparing IR spectrum of drug with reported spectrum of Verapamil Hydrochloride . The characteristic absorption bands in the infrared absorption spectrum of Verapamil Hydrochloride and a summary of the description of the characteristic IR bands for Verapamil Hydrochloride are described.

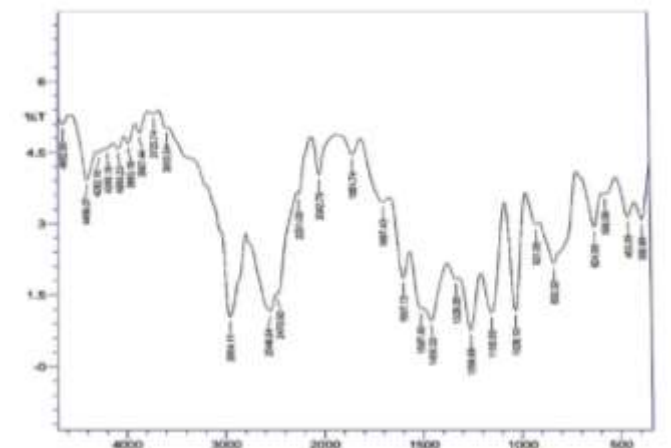


Figure 6: FTIR of verapamil hydrochloride

Table 7: FTIR interpretation of Verapamil Hydrochloride

Sr No	Functional Group	Theoretical Peaks (cm <sup>-1</sup> )	Practical Peak (cm <sup>-1</sup> )
1	H-Cl	2100-2500	2549.04
2	N-H	3500-3100	3593.54
3	C-H	3300-2700	2954.71
4	C=O	1650-1850	1687.43
5	C≡N	1380-1415	2251.02

### 6.2. Evaluation Parameter of Finished Product

#### 6.2.1. Physical Appearance

Table 8: Organoleptic Parameter

Batch Code	Colour	Odour	Texture
F1	White	Characteristic	Solid
F2	White	Characteristic	Solid
F3	White	Characteristic	Solid
F4	White	Characteristic	Solid
F5	White	Characteristic	Solid

Table 9: Physical Evaluation for Buccoadhesive tablet

Formulation Code	F1	F2	F3	F4	F5
Weight Variation	Pass	Pass	Pass	Pass	Pass
Uniformity of contents(mg)	98.36	98.98	98.11	98.98	98.48
Thickness	3.06±0.057	3.13±0.057	3.16±0.057	3.13±0.11	3.23±0.057
Friability	0.49	0.30	0.49	0.49	0.39
Hardness	6.87±0.035	7.4±0.141	6.75±0.070	6.47±0.035	6.87±0.035
Buccoadhesive Strength	22.6	19.7	24.1	20.1	30.9
In vitro release study	83%	87%	79%	75%	73%

The Batch F2 Shows Optimize Result.

### RESEARCH OUTCOMES

The majority of drugs are first pass cleared in the liver after administration, which prevents them from being transported efficiently via the traditional route and results in a lack of a significant correlation between mucosal membrane, permeability, absorption, and bioavailability, according to data from the most recent literature. Medication's bioavailability is increased when it enters the systemic circulation through the internal jugular without passing through the first pass clearance via hepatic enzyme processing.

Buccoadhesive formulations may work well in place of conventional drugs since they may freely bond to the buccal membrane. The direct acting vasodilator anti-hypertensive medication VPH is effectively absorbed from the gastrointestinal tract, however its bioavailability was low. Due to its convenient dosing and lack of unpleasant smells or scents, this form of administration is fantastic for buccal administration. The current study's objective was to create and evaluate buccoadhesive VPH tablets to improve oral bioavailability.

### CONCLUSION

The preparation of a buccoadhesive tablet proved successful. in order to prevent the first pass metabolism. Calcium channel blocker and class 4 antiarrhythmic verapamil hydrochloride. It functions by calming the heart's and blood vessels' muscles. Verapamil hydrochloride buccoadhesive tablets were made in five batches. F2 batch produces the best results in vitro when compared to other formulations among the manufactured batches of the tablets tested based on performance with respect to physical appearance, weight fluctuation, uniformity of content, thickness, friability, and hardness. According to an in vitro drug release research, formulation F2 had the best drug release of any other formulation, making it the best formulation overall. The results for every parameter were satisfactory.F2 batch thus discovered optimization.

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### CONFLICT OF INTEREST

The authors have no known conflict of interest concerning the present article.

## ABBREVIATIONS

VRH:- Verapamil Hydrochloride

HEC:- Hydroxy Ethyl Cellulose

Na-CMC:- Sodium Carboxy Methyl Cellulose

HPMC:- Hydroxy Propyl Methyl Cellulose

FTIR :- Fourier transform infrared

KBr :- potassium Bromide

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