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Formulation and evaluation of mucoadhesive nasal films of Quetiapine fumarate

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ABSTRACT

Nasal drug delivery has acquired attention as a hopeful alternative to oral administration due to its potential for rapid onset of action and avoidance of hepatic first-pass metabolism. This study presents a novel formulation of quetiapine fumarate as nasal films, aiming to improve drug bioavailability and patient compliance. The nasal films were prepared using a combination of hydroxypropyl methylcellulose (HPMC) and poly vinyl pyrrolidine (PVP) as polymers, with varying concentrations of quetiapine fumarate. The films were characterized for their physicochemical properties, including thickness, folding endurance, drug content, and in vitro drug release profile. Furthermore, the nasal films were evaluated for their mucoadhesive properties and ex vivo permeation across porcine nasal mucosa. The results demonstrated that the nasal films exhibited good mechanical strength, uniform drug content, and sustained drug release characteristics. The mucoadhesive properties of the films ensured prolonged contact with the nasal mucosa, leading to enhanced drug permeation. Overall, the formulation of quetiapine fumarate as nasal films presents a promising approach for improving drug delivery efficiency and patient adherence in the treatment of schizophrenia.

Keywords: schizophrenia, Quetiapine fumarate, mucoadhesion, bioavailability, patient compliance, nasal films.

INTRODUCTION

A complex mental illness that alters thoughts, feelings, and behaviour is schizophrenia. It can be challenging to manage, but with treatment, many people with schizophrenia can lead fulfilling lives.[1] Schizophrenia affecting

approximately 1% of the global population, is a chronic and severe mental disorder. It deeply impacts a person's thoughts, emotions, and behaviour. The disorder is characterized by positive symptoms like hallucinations and delusions, negative symptoms including disrupted emotions, and cognitive challenges. [2]
Quetiapine fumarate, a second-generation antipsychotic agent classified under dibenzothiazines, is prescribed for schizophrenia, bipolar disorder, and major depressive disorder. It primarily targets cerebral serotonergic (5HT2A), histaminergic (H1), and dopaminergic D1 and D2 receptors, with moderate affinity for 1 and 2-adrenergic receptors, and minimal affinity for muscarinic M1 receptors. [1]

Quetiapine fumarate has low systemic bioavailability i.e. 9 % and short half-life because of extensive pre systemic metabolism.[3] The focus of this study is to enhance the bioavailability of quetiapine fumarate (QF) by formulating it into mucoadhesive nasal films. This formulation aims to improve bioavailability, bypass first-pass metabolism, reduce dosage, and prolong the drug's action. [1]

Nasal films are thin, flexible strips that are designed to delivery medication through the nasal route. They are typically made from polymers such as hydroxypropyl methylcellulose (HPMC) or polyvinyl alcohol (PVA) and contain the active pharmaceutical ingredient (API) along with other excipients [3]

Intranasal delivery is a non-invasive mode of administration due to its potential for targeted delivery to the brain. The olfactory and trigeminal nerves serve as the anatomical foundation for the nasal cavity's relationship to the central nervous system (CNS). The high vasculature of the respiratory area enables systemic absorption avoiding possible hepatic metabolism. [4]

The current study developed a nasal film containing hydroxypropyl methylcellulose [HPMC], poly vinyl pyrrolidine [PVP] with propylene glycol as a plasticizer and permeation enhancer, respectively. This film was designed for nose-to-brain delivery of Quetiapine fumarate (QF). Our studies, including in vitro and ex vivo evaluations, demonstrated the film's adequate stability, mucoadhesion properties, and QF permeation across the nasal mucosa barrier. Moreover, the film's thickness and flexibility are suitable for intranasal application. [5]

MATERIALS AND METHODS

- Drug - Quetiapine Fumarate
- Plasticizer - Propylene Glycol (30%)
- Solvent – Ethanol (70%)
- Polymers - Hydroxypropyl methylcellulose (HPMC 15 cps and 50 cps) were produced from CDH Laboratories, New Delhi
- Polyvinyl pyrrolidine (PVP).

All other chemicals used were of analytical grade.

CALIBRATION CURVE [6]

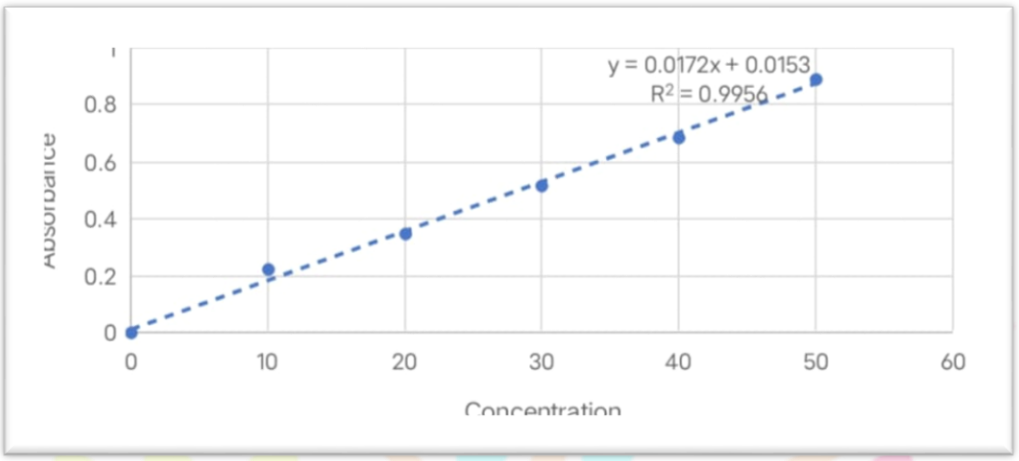
Standard curve of quetiapine fumarate of different concentrations is obtained. A concentration -dependent increase in absorbance was achieved in accordance with Beer lambert's law and a standard curve of quetiapine fumarate at various concentrations was generated. The resulted curve is displayed below.

S.NO	CONCENTRATION (mg)	ABSORBANCE
1.	0	0
2.	10	0.224
3.	20	0.35
4.	30	0.519
5.	40	0.69
6.	50	0.8921

PREPARATION OF THE STANDARD SOLUTION [7]

The standard solution of quetiapine fumarate was prepared by dissolving accurately weighed 20mg of quietapine fumarate in 20ml of 0.1 N HCL solution to get concentration of 1000µg /ml. A series of 20 ml volumetric flasks were filled to capacity with various aliquots of the above solutions ranging from 0.2 to 0.6 ml. The volume was then adjusted with 0.1N HCL. to obtain concentrations 10-30 µg/ml . The absorbance of these drug solutions were measured at 254.7 nm. Plotting the calibration curve as concentration vs. absorbance

FIGURE1: standard curve of quetiapine fumarate

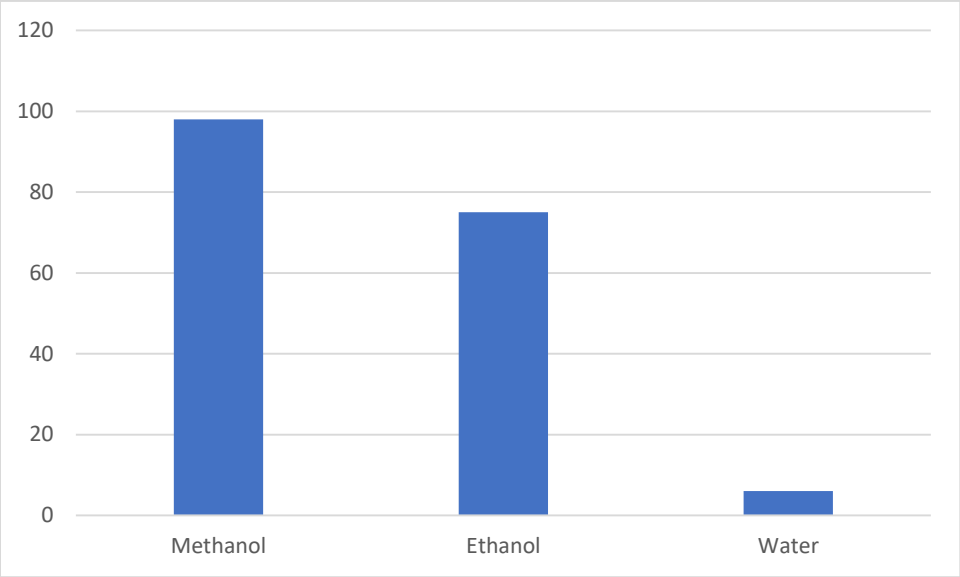


METHODOLOGY

1. Solubility analysis of Quetiapine Fumarate

s.no	Test	Observation	inference
1.	Quetiapine fumarate in Methanol	Clear solution is formed	Completely soluble
2.	Quetiapine fumarate in Ethanol	Solution is formed	Slightly soluble
3.	Quetiapine fumarate in Water	White precipitate is formed	Completely insoluble

➢ Ethanol is selected as a suitable solvent in this process because both drug and polymer are soluble in ethanol and it shows effective results in formulating a film.



2. Method of solvent casting technique

Selection of solvent system

↓

Preparation of polymeric solution/ suspension

↓

Casting of polymeric solution/ suspension

↓

Drying of casted solution/ suspension in a hot air oven at 40-50°C

↓

Peeling, cutting and packing of prepared film.

PREPARATION OF FILMS [8,9]

- Solvent evaporation technique / solvent casting technique was used to explore the current preparation of quetiapine fumarate nasal films.
- By using solvent evaporation technique/ solvent casting technique we prepare the films. By using various polymers such as HPMC and PVP of various composition, 30% propylene glycol as a plasticizer, 70% ethanol as a solvent.

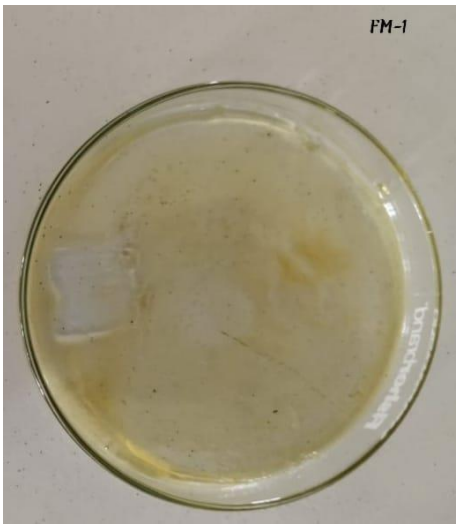
SOLVENT CASTING TECHNIQUE: [8,9]

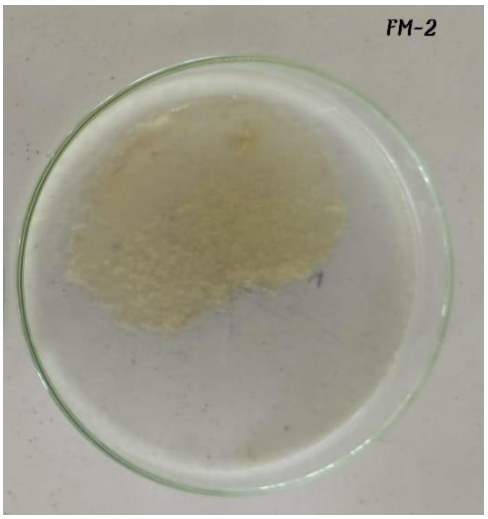
- The films of quetiapine fumarate were prepared using solvent casting technique.
- Polymers are dissolved in the suitable solvent.
- 20mg of quetiapine fumarate is dispersed in polymeric solution of hydroxypropyl methyl cellulose (HPMC) and poly vinal pyrrolidine (PVP) in different concentrations.
- Add propylene glycol which acts as plasticizer as well as penetration enhancer.
- Mix the solutions until it gets semi solid consistency.
- To remove the air bubbles in the solution is sonicated in bath sonicator.
- The films were placed on the petri dish and cover it with funnel to control evaporation.
- Shade dries it at room temperature overnight.
- After drying films were separated and packed in aluminum foils.

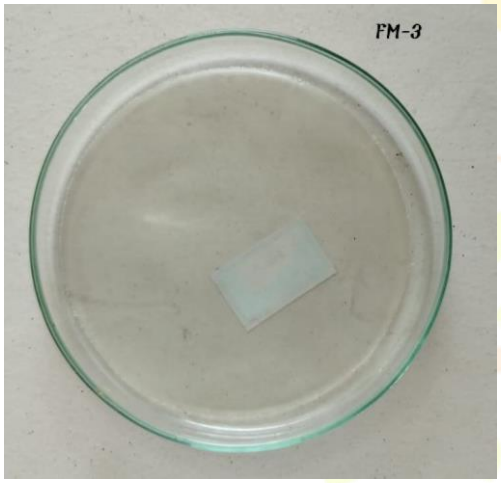
Storage conditions: store in desiccator at room temperature and 58% relative humidity

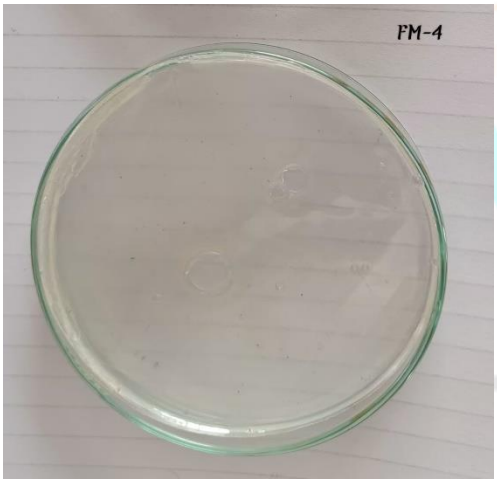
TABLE.1:

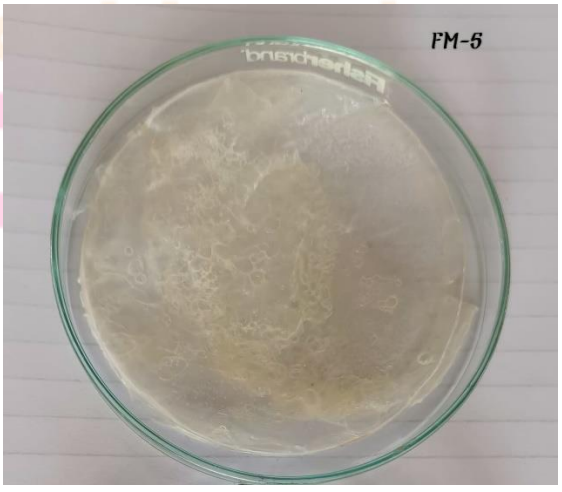
S.NO	FORMULATION CODE	DRUG [QUEITIPINE FUMARATE]	HPMC [POLYMER]	PVP [POLYMER]	PROPYLENE GLYCOL	ETHANOL
1.	FM1	20mg	0.5gm	1.5gm	0.5ml	10ml
2.	FM2	20mg	1gm	1gm	0.5ml	10ml
3.	FM3	20mg	1.5gm	0.5gm	0.5ml	10ml
4.	FM4	20mg	2gm	-	0.5ml	10ml
5.	FM5	20mg	-	2gm	0.5ml	10ml


FM-1


FM-2


FM-3


FM-4


FM-5

EVALUATION OF FILMS

1. Film weight and thickness: [8]

- The weight and thickness of the films were measured by taking three films from each formulation.
- For weight, the films were individually weighed using a digital balance, and the average weight of the three films was recorded.
- For thickness, three films were measured using a Digital Vernier Calliper at six different locations, and the mean thickness value was calculated.

2. Folding endurance: [9]

Folding endurance is evaluated by cutting films to the correct size and folding one film repeatedly in the same spot, up to 300 times, until it breaks. If the film doesn't break after multiple folds, it indicates strong folding endurance.

3. Surface PH: [10]

The surface pH of films was tested by preparing a solution of 2% w/v agar in isotonic phosphate buffer with a pH of 6.8. This solution was poured into a Petri dish and left to solidify at room temperature. The films were placed on the agar surface and left to swell for 2 hours. The surface pH was then measured using pH indicator paper, which changed colour after 90 seconds. This colour change was compared to a standard colour scale to determine the PH.

4. Percentage moisture absorption: [8]

A 1cm diameter film was kept in a desiccator containing a saturated solution of aluminium chloride, maintaining a humidity of 79.5%. The films were left in the desiccator for 3 days, and the weight before and after this period was used to calculate the percentage moisture absorption.

It can be calculated by using formula

% moisture absorption = [(final weight – initial weight) /initial weight] x 100

5. Percentage Moisture Loss: [8]

A 1cm diameter film was kept in a desiccator containing a saturated solution of calcium chloride. The films were left in the desiccator for 3 days, and the weight before and after this period was used to calculate the percentage moisture loss.

It can be calculated by the formula,

Percentage moisture loss = (final weight – initial weight) /Initial weight x 100

6. Swelling percentage: [10]

Each films weighed separately, noted as (W1) and then placed in a Petri plate with phosphate buffer at pH 6.8. Once removed from the plate, any extra surface water is dried off with filter paper, and the film is weighed again and noted as (W2).

The swelling index (SI) is then calculated using the formula:

SI = [(W2 - W1)/W1] x 100

Where:

- SI stands for Swelling Index.
- W2 denotes the final weight.
- W1 is the initial weight.

7. Drug content uniformity:

The drug-containing films are cut into three equal pieces. Each piece is then treated individually with a phosphate buffer solution at pH 6.8 for 24 hours. After that, the samples are analysed using a UV spectrophotometer at a wavelength of 296nm to measure the drug content. The average drug content from the three pieces is taken as the final result.

8. Invitro disintegration time: [10-12]

A pharmaceutical film can be assessed by placing it in a Petri dish containing 2 ml of distilled water. The dish is then rotated every 10 seconds, and the time it takes for the film to dissolve or break apart is recorded as the in vitro disintegration time.

9. Tensile strength of films: [9]

The entire force needed to tear the film is known as the tensile strength. A tool made of plexiglass with two plates, one that can move and the other fixed, is used to measure this strength.

It is calculated with formula,

TS = Breaking load / cross sectional area of the film

10. Mucoadhesive ability of films: [11]

The films' ability to stick to the mucosa was tested by placing sheep mucosa tissue on glass slides at a 60° angle. The adhesion of the films to the tissue was observed at different times (15, 30, 45, 60, 75, 90, 105, and 120 minutes after application), which aligned with the timeline of the permeation study.

11. **Ex vivo permeation studies**

A research experiment was carried out to examine how quetiapine fumarate penetrates sheep mucosa using a modified diffusion cell at a temperature of 37±1°C. The buccal mucosa was sandwiched between two compartments: the donor compartment, where the drug was applied, and the receptor compartment, which contained a solution with a pH of 6.8. The mucosa was fixed to an open-ended cylinder in the donor compartment, and the film containing the drug was placed to stick to the mucous membrane. The setup was maintained at 37°C and stirred with a magnetic stirrer. Samples were collected at regular intervals and analysed using UV-visible spectroscopy at a wavelength of 296 nm.

12. **IN-VITRO DISSOLUTION STUDIES:** [12]

The in-vitro dissolution studies were conducted using six basket dissolution apparatus at 37± 0.5ºC and at 50rpm.Each film of dimension (1-1cm) was placed on a stainless -steel basket. Dissolving media was poured over the film sample that was set up on the sieve.

Samples were collected at 0, 15, 30, 45, 60 minutes. Time intervals were filtered with 0.45µm Whatman filter paper and was analysed using spectroscopy at 296nm.To maintain the volume, an equal volume of fresh dissolving medium kept at the same temperature and was added after the samples were removed. The absorbance data has been converted to concentration using a standard calibration curve previously established through experimentation**.**

Ph:6.8

Buffer: Phosphate buffer(900ml)

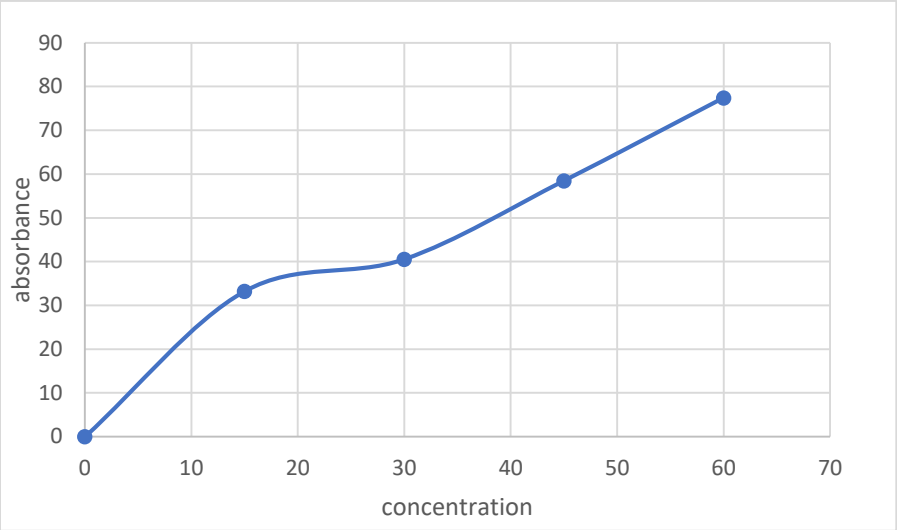
Film Size:1x1cm

Temperature:37±0.5ºc

Speed:50rpm

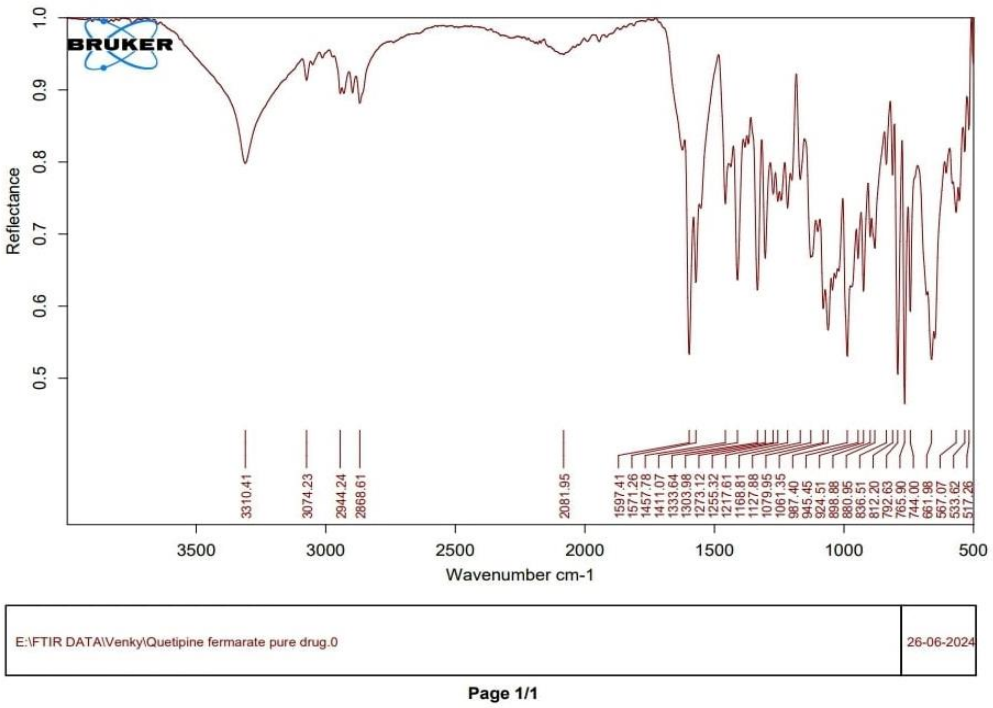
Table2

Time interval(min)	Fm-3
0	0
15	33.21
30	40.53
45	58.46
60	77.40

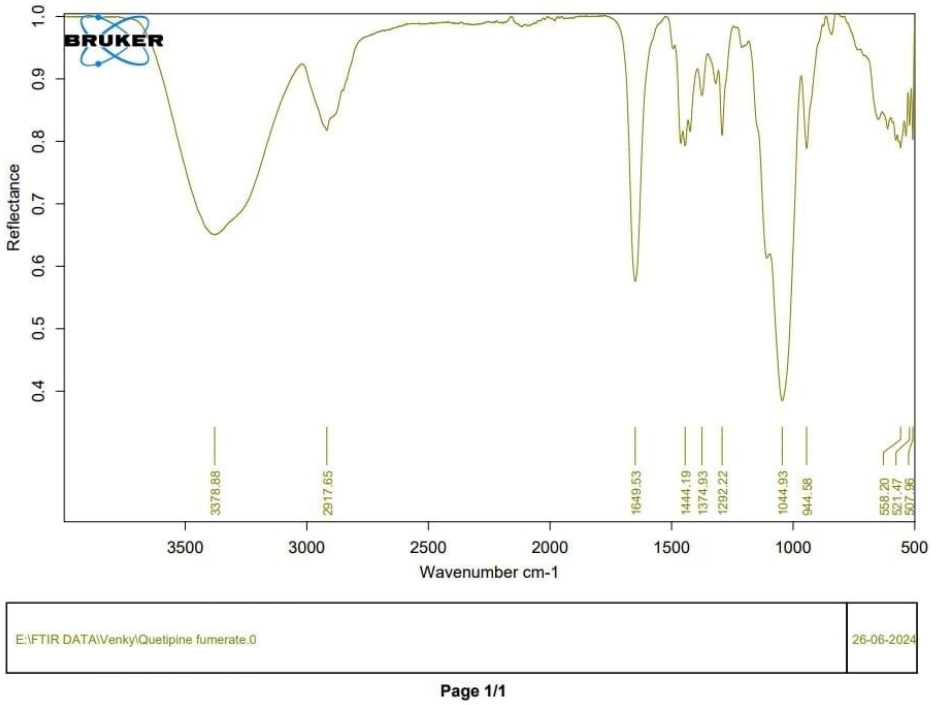


DRUG POLYMER COMPATIBILITY STUDIES

Drug polymer compatibility studies are performed by Fourier transform infrared spectroscopy (FTIR), in order to confirm there is no interaction between drug and polymer. Pure drug and all polymer used like HPMC, PVP and their combinations are analysed.



FTIR spectrum of Quetiapine fumarate pure drug



FTIR spectrum of Quetiapine fumarate and polymer formulation as films

RESULTS AND DISSCUSSION

1. Weight of the films

The weight of three films was examined by using digital balance.

The weights are found to be,

Weight of film(w1) – 28mg
Weight of film (w2) – 24mg
Weight of film(w3) – 24mg
The average weight of three films was found to be 25.33 mg.

2. Folding endurance

A film of 1x1 cm is taken and folded at same position. Cracks were not appeared even after 300 folds. It ensures the good folding endurance.

Result: crakes appear at 348 folds.

3. Mucoadhesive ability of films

Films are tested at regular time intervals for 120 minutes to observe the physical stability, colour change, shape of films.

4. Percentage moisture absorption:

The percentage moisture absorption of the film was found to be 15 %

5. Percentage moisture loss:
The percentage moisture loss of the film was found to be 20.8 %.

DRUG POLYMER COMPATIBILITY STUDIES

The spectral analysis of data has shown that there were greater values for optimized formulation mixture compared to pure extract. So, it was concluded that there was no interaction between drug and polymers.

CONCLUSION:

In conclusion, mucoadhesive nasal films represent a promising drug delivery system that offers several advantages over traditional routes. Their preparation involves the careful selection and combination of polymers, plasticizers, and active pharmaceutical ingredients to create a film that rapidly dissolves upon contact with nasal mucosa. Key preparation methods include solvent casting and hot-melt extrusion, each with its own set of advantages in terms of film uniformity and drug loading capacity.

Evaluation tests for these films performed. These comprehensive evaluations ensure that mucoadhesive nasal films are not only effective in delivering drugs but also safe and reliable for patient use. The rapid onset of action, ease of administration, and improved patient compliance make them a valuable option in the field of nasal drug delivery. Continued research and development in this area are likely to expand their applications and enhance their performance, potentially revolutionizing treatment regimens for various conditions.

In the present study, mucoadhesive nasal film containing quetiapine fumarate by solvent casting method using polymer hydroxyl propyl methyl cellulose, polyvinyl pyrrolidine and Plasticizer propylene glycol are prepared and evaluated. Of all the formulations, FM 3 shows best results. Formulation FM 3 is optimized with low concentration of polymers. Formulation FM 3 shows drug release within 3min which is very less than other formulations.

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