DESIGN AND DEVELOPMENT OF A FAST-DISSOLVING FILM OF TELMISARTAN

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ABSTRACT

The purpose of the study was to design and development of fast dissolving film of Telmisartan. Telmisartan is an anti-hypertensive agent which belongs to BCS class II with 24 hours half-life. Main objective is to increase the release time of the dosage form at the site of absorption thus leading to enhance absorption and bioavailability. There were six formulas made in total. The substance polyvinylpyrrolidone is used to create films. As plasticizers, propylene glycol and polyethylene glycol 400 were employed. FTIR spectra of the physical mixture revealed that the drug is compatible with polymers used. This system was developed by using Solvent Casting Method. The homogeneity of the content, thickness, folding durability, disintegration time, and dissolution tests of the films were assessed. Out of all the formulations, F4 demonstrated improved bioavailability and good physicochemical properties.

KEYWORDS: Fast Dissolving Film, Telmisartan, Propylene glycol, Polyethylene

INTRODUCTION

Oral administration is the most popular route due to ease of ingestion, pain avoidance, versatility (to accommodate various types of drug candidates), and most importantly, patient compliance. [1] Furthermore, because they don't require sterile conditions, the production of solid oral delivery systems is less expensive. To improve patient compliance and address the physicochemical and pharmacokinetic characteristics of medications, some innovative technologies [2] for oral delivery have recently become accessible. Other recent advances include tablet manufacturing, electrostatic drug deposition and coating, and computer-assisted three-dimensional printing (3DP).

Fast-dissolving drug delivery devices were first developed in the late 1970s to give elderly and pediatric patients who have difficulty swallowing traditional oral solid-dosage forms an option to tablets, capsules, and syrups. The terms "fast dissolve," "rapid dissolve," "rapid melt," and "quick disintegrating tablet" refer to the revolutionary oral fast dispersing [3-5] dosage forms technology. Nonetheless, all of these dose forms have a similar principle and purpose.

An oral fast-dispersing dosage form is, by definition, a solid that, in the oral cavity, dissolves or breaks down quickly to produce a suspension or solution, all without the need to deliver water. Dysphasia, or difficulty swallowing, is a common condition affecting people of all ages, but it is more prevalent among the elderly. Those who use normal tablets and capsules may also be affected. Dysphasia is associated with many medical conditions, including stroke,

Parkinson’s, AIDS, thyroidectomy, head and neck radiation therapy, and other neurological disorders, including cerebral palsy. Form, surface, and flavor were the most often mentioned concerns, then tablet size. Tablet ingestion was more challenging for older and pediatric patients, as well as for patients who were traveling and might not have had easy access to water.

Oral disintegration tablets (ODT), wafers, and the most recent invention of oral films (ODF), which can be thought of as an ultra-thin strip the size of a postage stamp that contains an active agent or active pharmaceutical ingredient and other pharmaceutical excipients, are the results of research and development in the oral drug delivery segment. Due to the ease of dosing probability of ODF, both the pediatric and geriatric populations have come to adopt this dosage form more widely.

As a nonpeptide angiotensin receptor II antagonist and antihypertensive medication, telmisartan (TLM) inhibits the effects of angiotensin II on vascular smooth muscle and is used to treat hypertension symptoms. Its poor solubility in water is the main disadvantage of this medication. Due to its insoluble nature in water, the medication may dissolve slowly or in part in the gastrointestinal tract. Significant first-pass hepatic metabolism is the reason for TLM's low bioavailability (around 45%).

MATERIALS AND METHODS

Telmisartan was purchased from Balaji Drugs, while Research Lab Fine Chemicals in Mumbai provided the polyvinylpyrolidine K-15 and polyethylene glycol 4000. The supplier of Eudragit L-100 was Evonik Industries in Mumbai. We purchased HPMC-K15 and HPMC K-4 from Colorcon Asia Pvt. Ltd. in Goa. All materials and chemicals used were of analytical grade.

Drug-Polymer Compatibility Studies

Drug Content

The careful selection of excipients additions made to a solid dosage form to aid administration, support the drug's uniform release and bioavailability, and shield it from degradation is essential to the formulation of a stable and effective solid dosage form.[7] The drug content percentage was computed using the standard graph, and each formulation underwent three UV-Spectroscopy runs.

IR spectrum study

To investigate the potential drug-excipient interaction, FT-IR was performed. [8]

Formulation and Development of fast dissolving films

Telmisartan oral films were made using the solvent casting technique. A 9.5 cm diameter glass Petri plate was used as casting surface. Accurately weighed Telmisartan (equivalent to 708 mg of Telmisartan) was dissolved in 10ml of DW using mechanical stirrer for 30 mins. Further required quantity of PVP K-15, PEG 4000, Eudragit L-100 (as per need) and Citric acid were added with constant stirring into same solution. HPMC K-4 and HPMC K-15 was dissolved in 10 ml of DW separately and was kept in refrigerator for the purpose of cooling (since HPMC dissolves in cold water) for 2-3 hrs. After that, a mechanical stirrer was used to combine the two solutions until a clear solution was achieved. Later propylene glycol (10-20% w/w of polymers) was added as a plasticizer with constant stirring for 10-15 min. The resultant solution was then casted on the glass Petri plate and allowed to dry in a hot air oven, maintained at 40°C for 6 hrs. Finally the dried film was cut into the size of 2 cm x 2 cm, with total surface area of 4 cm^2, so that each film contains desired amount of drug (40 mg). [9] The samples were packed in aluminium foil and stored in amber colored glass container. They were kept at room temperature and 60 % RH: so that the integrity and elasticity of films was maintained.

Evaluation of fast dissolving film:

The following characteristics of the Telmisartan quick dissolving films were assessed:

Physical Appearance and surface texture of film: Films of every formulation were chosen at random and examined visually for texture using touch or feel. [10].

Weight Variation: Film prepared was cut from different areas into 5 patches of 4 cm^2. Every patch is weighed and average weight is calculated. Next, the film patch's weight fluctuation was discovered. [11].

Thickness: A computerized micromatic caliper was used to measure the film's thickness, with a minimum count of 0.01 mm. [12].

Folding Endurance: The film was folded repeatedly from the same location until it broke or there were no visible breaks in order to measure folding durability. The number of times a film can fold without breaking is known as folding endurance. [13].

Surface pH Measurement: To find out if the film irritates the oral mucosa, the film's surface

pH was measured. [14]

Swelling Index: The swelled films were then weighed, and the formula below was used to calculate the selling index. [15]:

$$\text{Swelling Index SI} = 100\ (Wt - Wo)/\ Wo$$

Where Wt is weight of the film at time = t and Wo is weight of the film at t =0.

Disintegration time: A film's disintegration time is the length of time, in seconds, that it breaks when it comes into contact with water or saliva. Depending on the formulation Disintegration time varies but typically it ranges from 5 to 30 sec [16]. Using this procedure, the film is manually dipped in 10 cc of pH 6.8 phosphate buffer in a beaker and agitated every 10 seconds to determine the disintegration time. The temperature was kept at 37±2°C. When the film starts to break or disintegrates, time was noted.

Drug Content Uniformity: For this test, a patch of film was taken and placed in a beaker containing 100ml phosphate buffer pH - 6.8. For 6 hours, the medium was mixed on a magnetic stirrer to ensure proper dissolution. After that, the content was filtered via Whattman filter paper, and the filtrate sample was examined at a certain wavelength using a UV spectrophotometer to determine which drug was included in the film. By tracing a standard calibration curve of the medicine in a pH 6.824 phosphate buffer, the quantity of drug was determined. [17]

In vitro Dissolution test: The USP basket device was used for the in vitro dissolution test. In 500 milliliters of pH 6.8 phosphate buffer, at 37±0.5 oC and 50 revolutions per minute, the dissolving tests were carried out. The film size required for dose delivery (2 × 2 cm2) was used. Five milliliter aliquots of the dissolving medium were taken at intervals of 2, 4, 6, 8, 10, and up to 12 minutes. A UV spectrophotometer was used to filter the obtained sample and measure the amount of Telmisartan in the film at a wavelength of 289 nm. [18].

Accelerated Stability Studies:

The purpose of the stability experiments, which followed ICH recommendations Q1A, was to find out how temperature and relative humidity affected the medicine in various formulations. The oral dissolving films were kept in stability chamber, at 40± 0.5°C temperature and 75±5% RH for 2 months respectively. After 1, and 2 months, oral films were tested for Changes in the appearance, Drug Content, Change in surface pH, Disintegration time. [19]

RESULTS AND DISCUSSION

Drug content:

It can be presumed that there was no interaction between the medication and the chosen excipients because there was no discernible difference between the drug assay performed at the start and after 30 days.

Table No. 1: Determination of drug content from drug-excipients mixture

Compatibility Mixture	Assay of mixture (Initial)	Assay of mixture (After 30 days)
Drug + HPMC K-4	97.85	97.34
Drug + HPMC K-4	98.78	98.71
Drug + Propylene glycol	98.86	98.83
Drug + Citric acid	98.52	98.32

IR Spectrum:

For characterization of pure Telmisartan FTIR studies were carried out. The observed and reported characteristic peaks of functional group have been shown in IR spectrum.

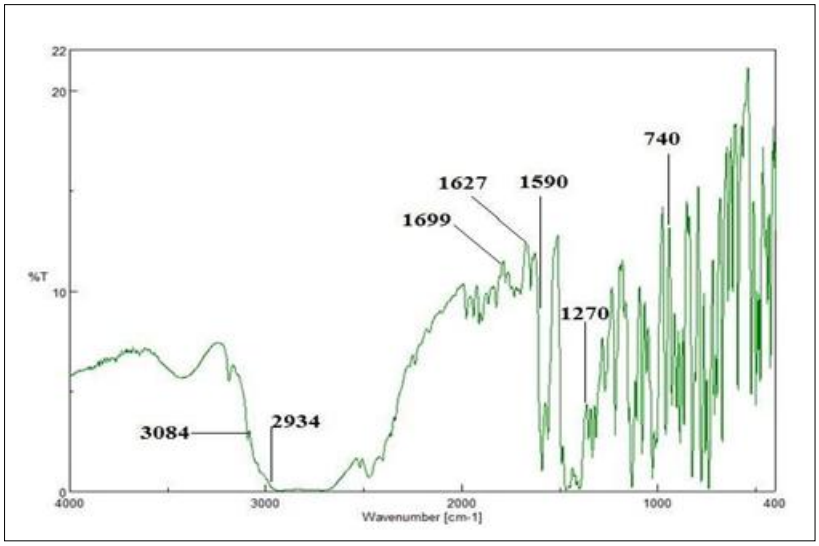

Figure No.1: IR Spectrum of Telmisartan (pure drug)

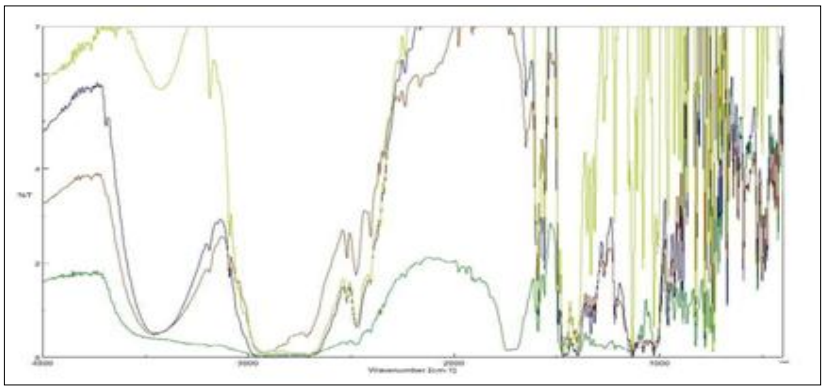

Figure No.2: overlay of Telmisartan (light green), Telmisartan + HPMC K-4 (green), Telmisartan + HPMC K-15 (blue), Physical mixture

(Telmisartan, HPMC K-4, HPMC K-15, Propylene glycol and Citric Acid).

Telmisartan and certain polymers did not interact, according to the drug-excipients interaction investigation, as there was no discernible shift in the peaks' IR spectra. Additionally, the IR spectra of drug-excipients and the physical mixture sample showed the distinctive peaks of the medicine Telmisartan. From these IR spectra, it was concluded that the selected excipients were compatible with drug Telmisartan.

Evaluation of fast dissolving film:

Physical appearance:

All films from F1 to F6 containing HPMC K-4 and K-15 as film former and PG as plasticizer were found to be smooth and elegant with transparent appearance.

Thickness:

According to the table, the average thickness of all ODFs varied from 0.07±0.67 to 0.17±0.92 mm.

Weight uniformity:

It was discovered that the weight variation values (mg) of the various Telmisartan films varied between 48.32±0.03-54.84±0.41 mg. As a result, the films' weight increased proportionately to their thickness. This shows how uniform the cast of the movie was.

Folding endurance:

It was shown that folding endurance increased with increasing HPMC content. This is because, when HPMC concentration increased, there was a corresponding rise in molecular mobility, leading to a reduction in resistance and an increase in flexibility.

Surface pH measurement:

It was discovered that all of the films had pH values between 6.70±0.02 and 6.96±0.01. Because there could be adverse effects in vivo, no mucosal irritation was anticipated from these produced films.

Table No. 2: Evaluation of physicochemical parameters of Telmisartan film

Formulation	Thickness (mm)	Weight Uniformity (mg)	Folding endurance	Surface PH
F1	0.07±0.03	48.32±0.03	173±1.02	6.86±0.03
F2	0.09±0.04	54.75±0.48	184±1.43	6.88±0.04
F3	0.13±0.08	47.84±0.24	190±1.94	6.70±0.02
F4	0.15±0.05	53.29±0.21	181±1.78	6.96±0.01
F5	0.17±0.06	54.84±0.41	184±1.53	6.78±0.01
F6	0.14±0.07	52.97±0.14	179±2.03	6.84±0.03

All values are mean ± SD, n=3

Swelling index:

Swelling index of all formulation found in the range of 0.86±0.71 - 3.0714±2.50%. Maximum swelling index was shown in F4 formulation.

Disintegration time:

The D.T. for each batch of film is shown in Table 6, which demonstrates that the F1 through F6 batches disintegrated in less than 30 seconds. the F4 formulation shows D.T. 8.2±0.65 sec.

Drug content uniformity:

The outcomes are shown in the Table. Since the drug content values of the same formulation did not differ noticeably, it may be concluded that the medication was dispersed uniformly throughout FDF.

Table No. 3: Evaluation of physicochemical parameters of Telmisartan film

Formulation	Swelling index	Disintegration time (sec)	Drug content uniformity
F1	1.42±1.15	22.6±0.51	86.5±0.2
F2	0.86±0.71	15.4±0.36	87.2±0.1
F3	2.58± 2.11	14.8±1.23	83.8±0.5

F4	3.07±2.50	8.2±0.65	91.3±0.2
F5	0.95±0.82	19.4±0.36	81.2±0.8
F6	1.30±1.05	14.5±0.21	82.9±0.6

All values are mean ± SD, n=3

***In- vitro* drug release studies:**

Drug release profiles in vitro are shown in Figure. For every oral dissolving film containing telmisartan, an instantaneous drug release was effectively observed. It fell between % and. The F formulation exhibited the least amount of drug release due to the low concentration of P, high percentage of HPMC, and water solubility of P. According to an in-vitro drug release study, mouth dissolving film's plasticizer content affects how much medication is released.

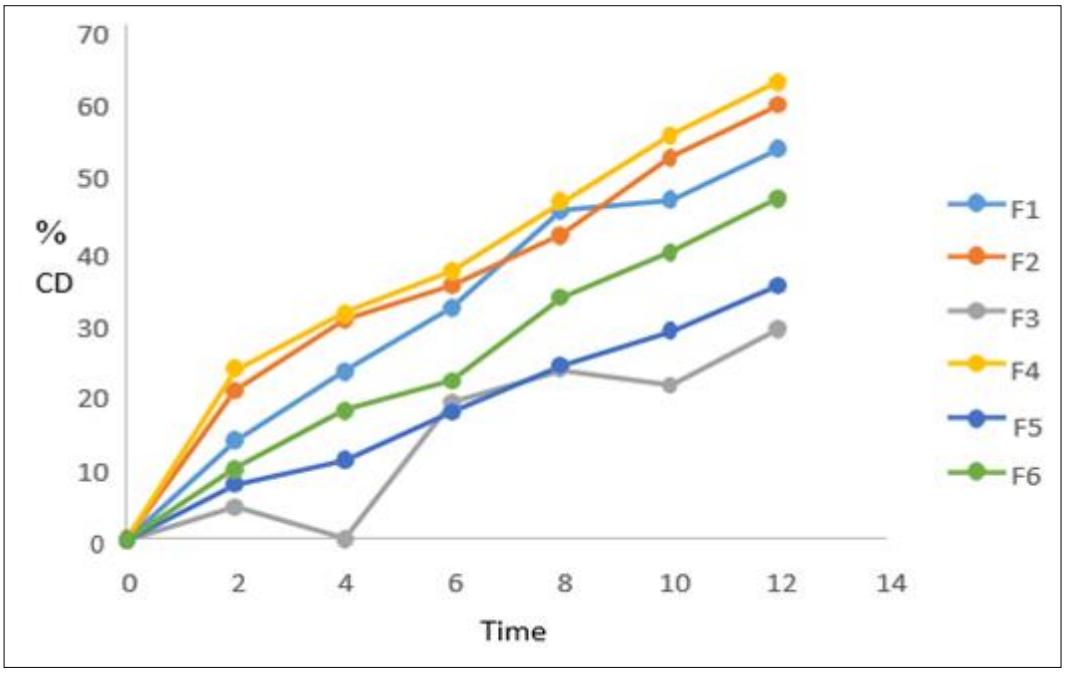

Figure No. 3: Comparative *in vitro* drug dissolution profiles of telmisartan fast dissolvingfilms

Accelerated stability studies:

According to ICH (QA R1) guidelines, batch F4 underwent an accelerated stability assessment for two months at 40°C±2°C and 75%±5 RH. The table displays the findings of stability tests performed on the upgraded batch. The results demonstrate that the film's appearance did not alter, and the disintegration time was hardly affected. The drug content

and surface pH both slightly decreased.

Table No.4: Stability studies of optimized batch at 40◦C±2◦C and 75%±5 RH.

Parameters	Initial	1 Month	2 Months
Appearance	No change	No change	No change
Drug content	91.3±0.2	90.8±0.4	90.5±0.5
Surface pH	6.96±0.01	6.93±0.03	6.89±0.05
Disintegration time (sec)	8±0.65	7. ±0.53	8. ±0.38

CONCLUSION

Using HPMC K-15 and HPMC K-4 as film forming polymers, telmisartan rapid dissolving films can be made with a quick release. It can be deduced from the current study that the medication becomes more soluble in PEG as its concentration increases. Each of the created films had a uniform weight, thickness, and drug content, and they all seemed smooth and well-maintained with no evident flaws. The F4 demonstrated good folding endurance, or 181, whereas the F3 displayed the highest folding endurance (190). According to stability experiments, there was no noticeable change in the physical properties of the F4 formulation while it was stored at 40 ± 2 ºC / 75 ± 5% RH.

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