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FAST DISSOLVING FILMS USING NATURAL AND SYNTHETIC POLYMERS CONTAINING DOLASETRON FOR THE TREATMENT OF ANTI-EMESIS

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ABSTRACT

The present study has been designed to develop, evaluate, and optimize Dolasetron FDFs (fast-dissolving films) through a solvent casting technique with the aim of increasing the bioavailability and patient compliance of Dolasetron. The formulations were made with hydroxypropyl methylcellulose (HPMC) and gellan gum, at different percentages of the polymers. Various parameters used in their evaluation included drug content, percent yield, in-vitro dissolution, thickness, weight change, percent elongation, folding stamina, swelling behavior, clarity, and disintegration time. In-vitro dissolution tests demonstrated that drug release was delayed as the polymer concentration increased and this was ideal with controlled-release formulations. These findings suggested that formulation F11, which comprised 10 mg of Dolasetron and the greatest concentration of polymer, exhibited desirable properties, including drug content uniformity (94.1%) and ideal drug release profiles. The FTIR revealed the absence of interaction between Dolasetron and excipients which demonstrated the stability of the drug in the formulation. The stability studies indicated that F11 was stable in terms of physical and chemical characteristics during the storage conditions with a sustained release of the drug and no marked variation in the assessment parameters. The conclusion of the study is that the developed Dolasetron FDFs may serve as a promising alternative to the traditional dosage forms, as the effective and stable means of the drug delivery, with the higher patient compliance and improved bioavailability.

Key words: Natural, Synthetic Polymers, Fast Dissolving Films, Anti – emesis

INTRODUCTION

Medicine tablets used to be shaped like disks that were colored according to their contents, but today they come in a variety of shapes and colors to make them easier to identify. A tablet may be engraved with symbols, letters, and numbers to identify it, or it may have grooves so that it can be split with a hand. The size of a tablet can range from a few millimeters to a few

prescriptions are distributed in form of solid dosage forms and the other half in the form of compressed tablets. It may be given sublingually, buccally, rectally, intravaginally or sublingually. Formulating tablets that deliver specific dosages to specific body areas is possible. The oral drug is also available in a variety of different forms such as syrups, elixirs, suspensions, and emulsions in addition to tablets (Patel VF, et al., 2011 & Hiestand EN, et al., 1997).

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centimetres. Today, compressed tablets are the most common form of medication. About 50 percent of all

Tablet properties

Tablets can be made in virtually any shape, but most are round, oval, or capsule-shaped to meet the needs

of patients and tableting machines. It is more difficult for patients to swallow unusual shapes, and they are more prone to chipping and manufacturing issues. During tablet production, a die, upper and lower punch, and machine tooling are used; these determine the diameter and shape of the tablet. The tooling station is also known as the tooling station. The thickness of a tablet depends on the quantity of the tablet material and the position of the punches in the compression. The measurement of the pressure during compression can therefore be used to measure the pressure applied. Short distances between punches cause greater compression pressure. Tablets should be hard enough not to break in the bottle, but soft enough to dissolve in the stomach. (Shangraw RF *et al.*, 1989)

Wet granulation

A liquid binder is used to lightly agglomerate powder mixtures during wet granulation. Granules that are overwetted will become too hard, and those that are underwetted will become too soft. Furthermore, aqueous solutions may not be as effective at hydrolyzing drugs as aqueous solutions. Wet granulation at low shear rates does not need complex mixing equipment and may be time consuming to mix uniformly. Wet granulation processes incorporate the mixing of powder and liquid very quickly using high shear equipment. Preheating, granulating, and drying powders in the same vessel is known as wet granulation. Thus, close control can be maintained during granulation.

Dry granulation

The dry granulation process creates granules by compacting powder blends under low pressure. A gentle breakup of compacted particles is necessary in order to produce granules (agglomerates). This process is often used to granulate products that are sensitive to moisture and heat. Slugging presses and roller compactors can be used for dry granulation. A wide range of pressures can be used on dry granulation equipment to achieve densification and granulation. There are several advantages to dry granulation over wet granulation in terms of simplicity and cost-effectiveness. Nonetheless, dry granulation can result in finer granules, which may result in a reduction in yield or a compromise in tablet quality. A 'dry binder' and excipients with cohesive properties must be included in the formulation. (Khan KA, *et al.* 1975)

Fast dissolving films

Pediatric and geriatric patients who have difficulty swallowing have an alternative to traditional oral solid dosage forms in the form of fast dissolving tablets developed in the late 1970s. With the use of superdisintegrants and hydrophilic ingredients, it is highly bioavailable, fast acting, and more patient-friendly. As a

matter of fact, fast dissolving tablets are often prepared by the expensive lyophilization method, which can be difficult to store, handle, and carry due to its fragility and friability. Furthermore, fast dissolving tablets can be difficult to swallow (Deshpande RD, *et al.* 2011 & Shah RB, *et al.*, 2008)

Advantages of Fast Dissolving Films

- No choking or obstruction risk.
- The lack of water has led to better acceptance among dysphagic patients
- Drugs are more bioavailable when taken orally
- Masking the taste
- Stability has been enhanced

Fast dissolving film manufacturing methods

The following methods are used to manufacture fast dissolving films. Fast dissolving films can be manufactured using the following processes:

- i. Solvent casting method
- ii. Semisolid casting method
- iii. Hot melt extrusion
- iv. Solid dispersion extrusion
- v. Rolling method

Solvent casting is generally used to manufacture strips (Morais J, *et al.*, 2014 & A.O. Surov, A.P *et al.*, 2016).

MATERIALS AND METHODOLOGY

Standard solution of Dolasetron (100µg/ml)

A volumetric flask containing 25ml of methanol was filled with approximately 25mg of the drug. Methanol was added to make up the volume. Using a volumetric flask of 10 ml, 1 ml of this solution was diluted in 10 ml of methanol. The solution contained 100 µg of drug per ml.

Determination of λ max and Calibration curve

The standard stock solution was placed into a volumetric flask measuring 10 ml, and 1 ml was added to the flask. There was a small amount of methanol added to make up the volume of the mixture. A concentration of 10 µg/ml of this drug was found in the solution at which it was present. This solution was compared with a blank solution of methanol in the UV range of 200 to 400nm in order to determine its absorbance in that range of wavelengths. A wavelength of approximately 277 nm was found to be the wavelength that was capable of capturing the maximum amount of absorbance.

Preparation of Calibration Curve for Dolasetron at 286nm

Standard stock solutions of 1, 2, 3, 4, 4.5, and 5 ml are pipetted into individual volumetric flasks of 10 ml. Methanol is used to top up the volumes to ensure that solutions are produced with concentrations of 10, 20, 30, 40, and 50 µg/ml. A graph between absorbance and

concentration was plotted using methanol as a blank and the resultant solutions were measured at 286 nm.

Method of preparation of SD

SDs were kneaded, physically and neutilization prepared in ratio of 1:0.5, 1:0.75 and 1:1 and compared in terms of drug content, percentage yield and dissolution character with physical mixture of the same.

Preparation of dolasetron FDFs using solvent casting method

The formulation of dolasetron FDFs can be found. Initially, film forming polymers and plasticizer were dissolved in water and, subsequently, other excipients containing the active pharmaceutical ingredient were added to the prepared solution. HPMC grades were used in the formulation of formulations FH1-FH5, while gellan gum was used to form the polymers and glycerol was used as the plasticizer in formulations FG1-FG5. Formulation FHG was made by combining HPMC with gellan gum and stirring them together at 2000 rpm over 4 hours and then setting it aside to de-bubble at room temperature over 1 hour. Another solution was prepared by dissolving the other additives with API in a hydro alcoholic solution and add it slowly to the first solution. After completing the stirring process, the solution was kept aside until bubbles were no longer visible. The solution was then poured into Petri plates for air drying to obtain the film (Y.Han, *et al.*, 2019 & Sachin Gholve, *et al.*, 2018)

Evaluation

Determination of drug content

The SD equivalent to 10 mg of dolasetron was weighed precisely and transferred separately to a 50 ml volumetric flask. For dissolving dolasetron, methanol was diluted to a volume of 50 ml and sonicated to provide a volume of 50 ml. The amount of dolasetron was determined by using a spectrophotometer (ElicoUV-1700 UV/visible double beam spectrophotometer) at 284 nm after appropriate dilutions with pH 6.8 phosphate buffer. For each sample, the assay is repeated three times. Calculated the drug content (Abraham Linku, *et al.*, 2018 & Edenta Chidi, *et al.*, 2017)

Determination of percent yield

According to Equation 2, the percent yield of prepared SDs was determined using the total recoverable final weight of SD and the total original weights of the drug and carriers. (Reddymasu SC, *et al.*, 2007 & Mahesh Shinde *et al.*, 2018)

In vitro dissolution studies

The drug release from the prepared SD was studied using an eight-station dissolution rate tester (Lab India, Disso 2000) at 75 rpm and $37 \pm 0.5^\circ\text{C}$. Dissolution

fluid was phosphate buffer (900 ml) of pH 6.8. Aliquots were withdrawn at predetermined intervals and replaced with fresh media. A spectrophotometer was used to measure the absorbance of these solutions at 284 nm. A similar process was used for dolasetron FDFs.

Evaluation of dolasetron FDFs

Thickness

Vernier calipers can be used at different strategic locations to measure the thickness of the strip. Ascertaining uniformity in the thickness of the film is essential to ensure accurate doses in the strip.

Weight Variation

Tests on weight variation should be conducted with at least two pieces of film. The weight of each film piece should be recorded using an analytical balance.

Percent elongation

When stress is placed on a strip sample, it extends and this is referred to as strain. Strain of a strip is just deformation divided by its original dimension. Generally, the more the plasticizer in a strip, the higher the elongation.

Folding endurance

The folding endurance is found by repeated folding at the same point until the strip breaks. Folding endurance is computed by counting the amount of folds without fracturing a film.

Swelling property

Example of a film is weighed and put into a stainless steel wire mesh. The mesh with the film sample has to be immersed into 15 ml medium in a plastic container. The weight of the film was measured at a preset time interval once it had acquired constant weight.

Transparency

Transmittances of films were measured at 600 nm by placing the film samples on the internal side of the UV spectrophotometer.

Disintegration time

The formulated films were tested for disintegration using standard apparatus as specified in the reference pharmacopeias, using pH 6.8 phosphate buffer.

Fourier transform infrared (FTIR) spectroscopy

The interaction between drugs and excipients was determined using an FTIR spectrophotometer (FTIR-8400S, Shimadzu, Japan). Samples were put in the side KBr discs (1:100 ratio of test sample in KBr) and pressed at hydrostatic pressure of 5.2 N/m² approximately in 180 seconds. The scanning was done between 400 and 4000 cm⁻¹.

Stability studies

When the formulations were optimized, accurate weights were obtained and the samples put in glass vials and stored at 1-3 months and then assessed on physical parameters, drug content and drug release.

RESULTS

Determination of drug content

In vitro dissolution studies

In vitro dissolution was assessed on all the formulations. Since increase in concentration of the polymers, HPMC K15M and gellan gum increased film swelling, disintegration time was longer and the %drug release was retarded. At the low concentration, the disintegration time was reduced and the %drug release was found to be higher in 20 min. Therefore, a less concentrated polymer formulation was optimized and implemented in FDFs preparation in order to realize the objective of the current research work. Fig. 1 exhibits the drug release profiles. The data relating drug release were examined according to the models of equation of zero-order, first-order, Higuchi, and Peppas.

Fourier transform infrared (FTIR) spectroscopy

The spectra of SD exhibited the similar characteristic stretches found in pure drug like N-H stretch at 3373.92 cm^{-1} , asymmetric =C-H stretching at 3026.33 cm^{-1} , symmetric -C-H stretching at 2937.10 cm^{-1} , -C=C- stretch at 1559.17 cm^{-1} and C-Cl stretch indicating the presence of alkyl halide at 756.26 cm^{-1} . No other peak, however, was observed in the spectrum pointing to the absence of any chemical interaction between the dolasetron and -cyclodextrin [14,15].

Stability studies

When optimized formulation F11 was taken through stability studies, it performed well *in vitro*. They conducted the stability studies at room temperature on the physical properties, drug content and drug release of the FDFs. Table and Figure provide the results of these studies. The results therefore showed that no visible and physical alterations were detected on the frequency discrimination even after being stored. Weight variation, thickness, surface pH, folding endurance, swelling property, transparency, disintegration time, and elongation were observed to be same before and after storing at different time period. No significant difference in the drug release of the F11 FDFs was noticed. Thus, rather stable drug release properties of designed FDFs were observed.

Table 1: Calibration Curve of Dolasetron

Concentration	Absorbance
10	0.1
20	0.17
30	0.26
40	0.35
50	0.43

Table 2: Composition of formulations

Ingredients (mg)	FH1	FH2	FH3	FH4	FH5	FG1	FG2	FG3	FG4	FG5	FHG
Ratio of API: CD	10	10	10	10	10	10	10	10	10	10	10
Hydroxypropyl methylcellulose K15	16	14	12	10	8	-	-	-	-	-	4
Gellan gum	-	-	-	-	-	16	14	12	10	8	4
Citric acid	4	4	4	4	4	4	4	4	4	4	4
Sodium starch glycolate	6	6	6	6	6	6	6	6	6	6	6
Mannitol	4	4	4	4	4	4	4	4	4	4	4
Tween 80	4	4	4	4	4	4	4	4	4	4	4
Total weight	44	42	40	38	36	44	42	40	38	36	36

Determination of drug content

Table 3: Drug content

Formulation code	Drug content
F1	82.02 $\pm$ 0.65
F2	85.79 $\pm$ 0.45
F3	94.1 $\pm$ 0.61

Determination of percent yield

Table 4: Percent yield

Formulation code	Percent yield
F1	84.12±0.74
F2	86.04±0.45
F3	93.4±0.49

Thickness, Weight Variation, Percent elongation, Folding endurance

Table 5: Thickness, Weight Variation, Percent elongation, Folding endurance

Evaluation parameters	Thickness	Weight variation	% Elongation	Folding endurance
F1	0.22±0.12	59.01±0.02	70.21±0.31	245±0.24
F2	0.22±0.21	57.12±0.01	68.13±0.41	231±0.41
F3	0.22±0.14	58.31±0.04	55.64±0.51	327±0.27
F4	0.23±0.07	57.18±0.21	53.17±0.74	328±0.27
F5	0.22±0.14	58.31±0.04	39.12±0.61	275±0.59
F6	0.22±0.10	59.04±0.01	30.41±0.65	313±0.29
F7	0.22±0.12	57.31±0.21	60.08±0.41	297±0.87
F8	0.23±0.05	58.31±0.14	69.27±0.87	289±0.49
F9	0.22±0.02	58.22±0.20	65.04±0.21	282±0.62
F10	0.22±0.04	58.45±0.08	52.3±0.55	307±0.78
F11	0.22±0.03	58.13±0.31	27.34±0.29	293±0.27

Swelling property, Transparency, Disintegration time

Table 6: Swelling Property, Transparency, Disintegration time

Evaluation parameters	Swelling property	Transparency	Disintegration time
F1	0.42±0.14	Transparent	33.0±0.3
F2	0.64±0.04	Transparent	27.0±0.28
F3	0.45±0.06	Transparent	30.0±0.56
F4	0.78±0.05	Transparent	26.0±0.97
F5	0.76±0.08	Transparent	25.0±0.55
F6	0.49±0.03	Transparent	32±0.68
F7	0.68±0.05	Transparent	25±0.84
F8	0.75±0.05	Transparent	26±0.75
F9	0.59±0.02	Transparent	27±0.84
F10	0.84±0.04	Transparent	24±0.59
F11	0.86±0.06	Transparent	25±0.84

Figure 1: Calibration curve of Dolasetron.

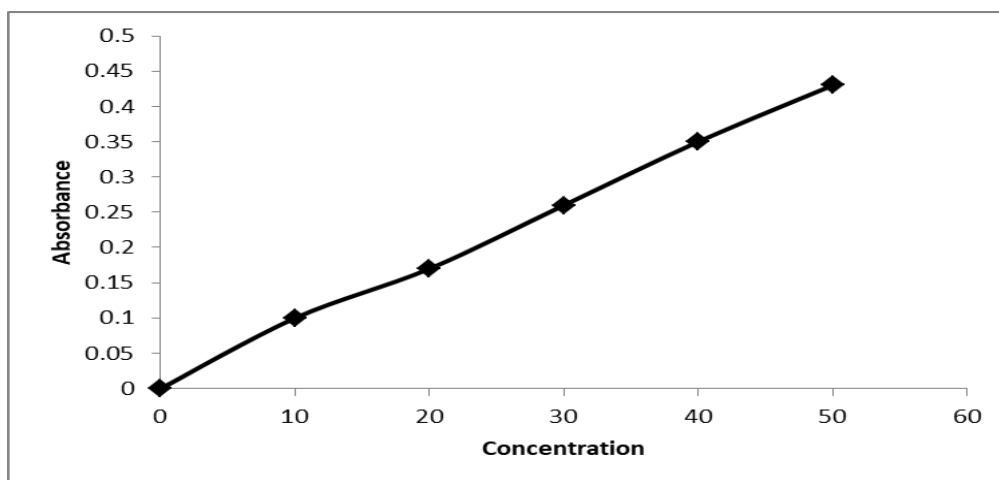


Figure 2: Zero-order Reaction

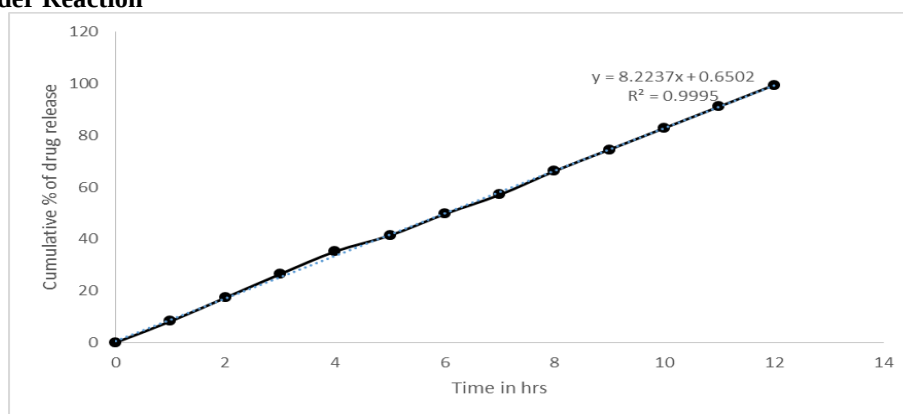


Figure 3: First-Order Reaction.

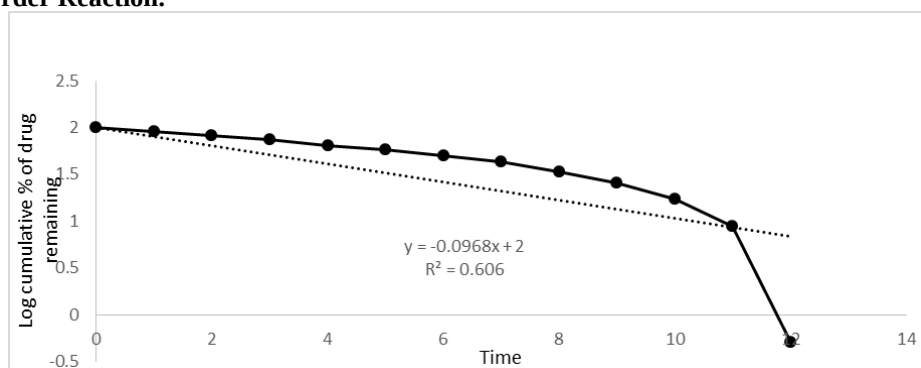


Figure 4: Higuchi Reaction.

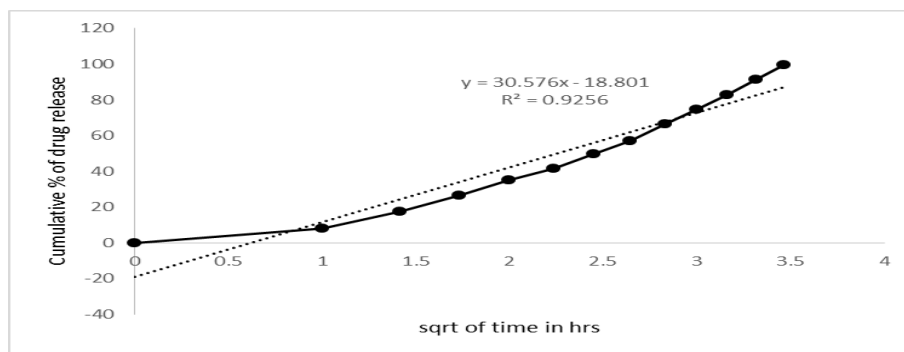


Figure 5: Fourier transform infrared (FTIR) spectroscopy.

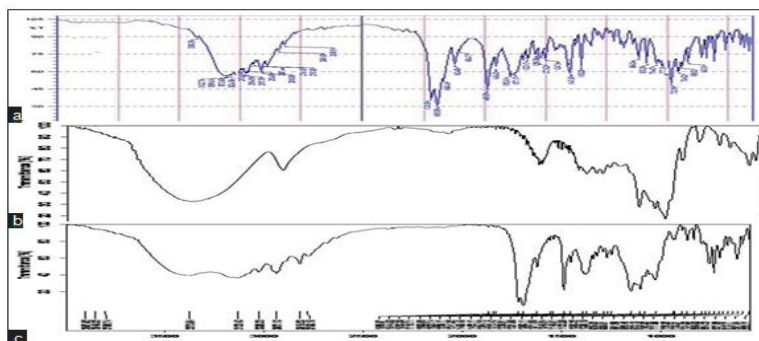
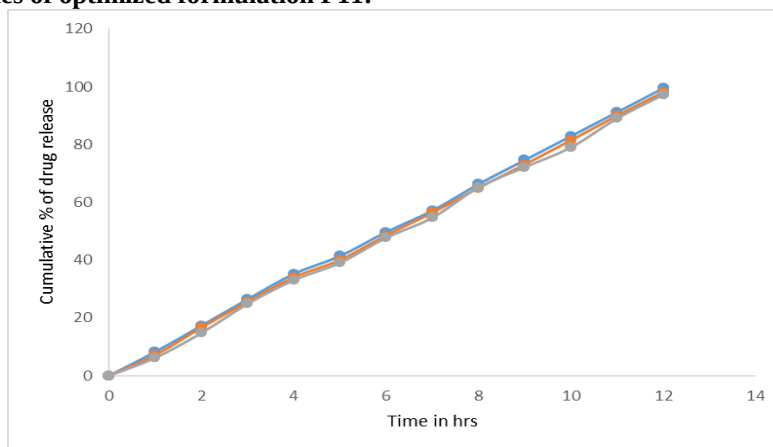


Figure 6: Stability studies of optimized formulation F11.



DISCUSSION

Dolasetron must be dosed correctly in every fast-dissolving film by monitoring its drug content. An indicator of the efficiency of the production process is the percent yield of the films. The success of a formulation process can be gauged by the consistency of the drug content and the production of a high yield for the drug. The drug content of the films was found to be consistent across batches, which indicates that the drug was distributed evenly within the films, indicating a good distribution of the drug. Dolasetron's release profile from the films will have to be determined by in vitro dissolution studies so that the release profiles can be evaluated. The films' rapid dissolution ensures that the drug is released rapidly in the oral cavity, leading to rapid

action. Dolasetron is released from these films within minutes of dissolution, so they are suitable for immediate release. Patient compliance and dosage uniformity are affected by the thickness and weight variation of the films. Consistent dosing requires uniform thickness and minimal weight variation. As evidenced by the minimal variations in thickness and weight, the films were manufactured precisely and reproducibly. A film's elongation percentage is used to assess its flexibility and tensile strength, while its folding endurance is used to assess its ability to resist repeated folding. Films with a high elongation and folding endurance value are robust and flexible, which are both important characteristics for handling and storing. Films with good mechanical properties are suitable for practical applications. The

swelling property of the film indicates its ability to absorb saliva and dissolve quickly in the mouth. A patient's acceptance of transparency depends on its aesthetic properties. Swelling properties of the films allowed for rapid disintegration and drug release. As well as being transparent, the films enhanced patient compliance. Fast-dissolving films require a rapid disintegration time because it determines how quickly the drug is released from the film in the mouth. Within a few seconds, the films disintegrated rapidly, indicating a fast-dissolving application. A study of potential interactions between dolasetron and polymers used in the film formulation was conducted using FTIR spectroscopy. According to the spectra, there are no significant interactions between the drug and polymers. As a result, the drug remains effective and stable within the matrix of the film. The shelf-life and storage conditions of the films were evaluated through stability studies. Various conditions were used to store the films, and the physical and chemical properties were monitored over time. Based on the results, the films were stable, and neither the drug content nor the dissolution profile of the films were significantly affected, indicating a long shelf life. The fast-dissolving films containing dolasetron, formulated using natural and synthetic polymers, exhibited excellent drug content uniformity, high percent yield, rapid dissolution, suitable thickness and weight variation, good

mechanical properties, and quick disintegration time. FTIR spectroscopy confirmed the compatibility of the drug with the polymers, and stability studies indicated the films have a good shelf-life. This makes the films an attractive treatment for anti-emesis, providing rapid onset of action and improved compliance among patients.

CONCLUSION

Fast-dissolving films containing dolasetron were formulated using both natural and synthetic polymers, which met the desired criteria for an effective anti-emetic dosage form. These are some of the key findings: The films enabled efficient and consistent production. Taking the films relieved nausea and vomiting quickly as dolasetron was released quickly. The films displayed a high degree of robustness and flexibility, allowing for easy handling and storage. The FTIR spectroscopy of the dolasetron did not indicate significant interactions with the polymers, and stability tests indicated that it would be stable for a long period of time. Fast-dissolving films are therefore a promising alternative to traditional anti-emesis dosage forms. Providing rapid onset of action, ease of administration, and patient friendliness, these films are an excellent addition to antiemetic therapy. These films may be subjected to clinical trials in the future to further validate their efficacy and safety.

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