ORIGINAL ARTICLE

Formulation and Evaluation of Sublingual Film Loaded with Granisetron Hydrochloride

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Abstract

Introduction: Sublingual films are well known for its rapid onset of action with enhanced patient agreement. The section of drug absorbed through the sublingual blood vessels by-passes the first-pass metabolism and the bioavailability of the loaded is improved considerably. Difficulty in swallowing, inaccessibility for water to swallow the conventional oral solid dosage forms and unexpected motion sickness are some of the situations that demand the development of sublingual films of Granisetron Hydrochloride. Objectives: To design and develop fast dissolving sublingual films of Granisetron Hydrochloride, with the prime objective to release the drug quickly from the film to facilitate oral absorption. Methods: The sublingual films of Granisetron Hydrochloride was prepared by solvent casting method and evaluated for weight variation and thickness of the film, folding survival test, visual appearance, disintegration time and in vitro dissolution. Results: A gradual increase in weight of the film was observed with increase in the concentration of the polymer. The observed disintegration time of the films was in the range of 13.40–13.64 Seconds. Folding endurance was found to be within the range of 71–77 which indicates that film has good flexibility. The formulation (B3) released about 86.42±0.23% of the Granisetorn hydrochloride within 105 seconds. Conclusion: The newly developed fast dissolving sublingual films of Granisetron Hydrochloride had exhibited faster release of the drug in the in vitro conditions with reliable strength and endurance.

Key words: Antiemetic, granisetron hydrochloride, hydroxypropyl methylcellulose, sublingual film

INTRODUCTION

Cancer: Worldwide, about 1 in 6 death, caused by cancer. In USA 1 out of every 17 deaths may be caused by lung cancer. An estimated around 222,520 people diagnosed with lung cancer in the US in 2010. Around 15 lakh new cases are diagnosed every year in India. Cancer is the second leading cause of death globally and is responsible for an estimated 9.6 million deaths in 2018. Approximately 60% of people being treated for cancer in the United States will receive radiation treatment.

Treatment of cancer

There may be different types of cancer treatment. These different types of cancer treatment may be depend on the types of cancer:

1. Chemotherapy
2. Immunotherapy
3. Hormone therapy
4. Radiation therapy
5. Surgery

Chemotherapy

Chemotherapy is a kind of malignancy treatment that utilizations medications to execute disease cells. Chemotherapy works by halting the faster cell divisions occurring in the malignancy. The types of treatment must depend on the types of cancer.

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The most common side effects of chemotherapy are as follows:

- Mouth sores
- Nausea
- Hair loss
- Fatigue.

Radiotherapy

Radiotherapy means malignant treatment which use high doses of radiation to kill cancer cells. Low levels of radiations do not kill cancer cells. It takes some time or week of cure before DNA is injured enough for cancer cells to die.

The most common side effects of radiation therapy are as follows:

- Fatigue
- Hair loss
- Nausea and vomiting
- Skin changes
- Headache
- Blurry vision.

Anti emetics

Antiemetics are a category of drugs that is efficient against vomiting and nausea. Antiemetics are typically used to treat motion sickness and the side effect of opioid analgesics and chemotherapy against cancer. Previously, before utilizing standard antiemetic drug regimens, nausea and vomiting resulted in up to 20% of patients in delay of chemotherapy. Profoundly, powerful antiemetic drugs are accessible these days and personal satisfaction.[1] However, in patients taking highly-emetogenic cytotoxic drug therapy, the proportion of patients experiencing effective antiemetic therapy is only 70–80% [Table 1].[2,3]

Sublingual film

Oral route is the most liked and adequate route due to ease of ingestion, pain avoidance, versatility and most importantly, and the patient compliance.[4]

Oral rapid disintegration films are an promising technology that brings out "formulations taken without water" with fast onset of action and better patient compliance.

Methods to produce sublingual film

A sublingual film is a slight film which may contain lively ingredient. A water-soluble polymers may contain different dissolving films which consist of following composition [Table 2].[5,6]

Active pharmaceutical agent

These drugs chosen for mouth films that to excellent solidity in saliva with less dose. These films have 0–24% w/w of the medicament. Multivitamins up to 20% w/w of waterless film weight has been incorporated with dissolution time of not more than 60 s.[7,8]

Film forming polymer

A range of polymers is obtainable for the preparation of fast-dissolving films. The polymers can be utilized alone or in a mix to get the ideal properties. The films received should be tough enough so that there may not be any harm even as handling or in the course of transportation.[9]

Plasticizers

Facilitates to get better the ability and reduces the weakness of the strip. Plasticizer may considerably improve the strip properties using decreasing the tumbler change over heat of the polymer.

METHODOLOGY

Preparation of fast-dissolving sublingual film

The films were set by the solvent casting method. A needed portion of a polymer is prepared by dispensing the polymer

Table 1: Different dosage form of antiemetic drugs used for chemotherapy

S. No	Drug name	Tablet	Capsule	Injection	Film	Dose
1	Aprepitant (emend)		✓			150 mg
2	Dexamethasone (dexpax)	✓				10 mg/ml
3	Dolasetron (anzemet)	✓		✓		20 mg/ml
4.	Granisetron (kytril)	✓		✓		1 mg/ml
5	Ondansetron (Zofran	✓		✓	✓	0.15 mg/kg
6	Palonosetron (aloxi)	✓	✓			0.25 mg
7	Prochlorperazine (compazine)	✓		✓		5 mg
8	Rolapitant (varubi)	✓		✓		(1.8 mg/ml)

in 20 ml of water with the help of continuous stirring. This preparing polymer being left for 3 h to eliminate air bubbles. After completion of polymer, drug, and as well as plasticizer and also other ingredients are mixed using a magnetic stirrer for 1 h. These polymer solutions may have allowed at room temperature for 24 h. The film is removed carefully and observed for imperfections and slice according to the size required for testing (square film 2 cm length, 2 cm width) so that every film consists1 mg of the drug [Table 3].[10,11]

Evaluation studies

Weight variation of the film

2 cm^2 films were sliced at five different areas in the caste film. The weight of each film was selected randomly weighed individually. The diameter is measured with a Vernier caliper.[12]

Table 2: Composition of fast-dissolving films

S. No	Composition	Size
1	Active pharmaceutical ingredient	0–24% w/w
2	Polymers	45–60%
3	Plasticizers	0–25%
4	Saliva stimulating agent	5–10%
5	Sweetening agent	5–8%
6	Flavoring agent	25%
7	Coloring agent	3%

Film thickness

The thickness of film formulation was determined using micrometer screw gauge. The film must be measured at five points, that is, from the center and from all the four corners, and then, mean thickness is calculated.[13]

Folding survival test

The frequent folding of films at a similar place until the strip breaks. The film is folding at the same place without cracking/breaking if it was folded up to 350 times manually without breaking which revealed the best endurance.[14,15]

Visual appearance

An film was checked visually, such as clear and translucent nature of film.[16]

Disintegration time

Disintegration time shows a sign about the disintegration characteristics of the film. Required size of the film is 2 cm × 2 cm of selected formulations which were placed in a glass Petri dish which contains 10 ml of stimulated saliva and left undisturbed.[17]

In vitro dissolution

The dissolution profile of quick-dissolving films of granisetron hydrochloride was carried out using USP type II

Table 3: Preparation of fast-dissolving sublingual films

Formulation code	HPMC E15 (mg)	HPMC E5 (mg)	Pullulan	PVP	Glycerol (ml)	Propylene glycol 400 (ml)	Water
F1	400			100	5		100
F2	350			100		50	100
F3		100			5		100
F4		75				50	100
F5			500	50	5		100
F6			450	50		50	100

Table 4: Composition of granisetron-loaded film

Formulation code	Drug (mg)	HPMC E15 (mg)	Pullulan	Propylene glycol 400 (ml)	Flavor (ml)	Aspartame (mg)	Water
S1	1.2	500		1	0.6	40	100
S2	1.2	750		1	0.6	40	100
S3	1.2		500	1	0.6	40	100
S4	1.2		750	1	0.6	40	100

Table 5: Evaluation parameters of sublingual films

Formulation rule	Weight (g)	Thickness (mm)	Disintegration (s)	Folding endurance	Visual appear
A1	0.018±0.003	0.15±0.02	5.03±0.03	15±1	Clear
A2	0.025±0.001	0.39±0.01	7.31±0.02	76±2	Clear
A3	0.040±0.004	0.60±0.02	11.17±0.02	55±2	Not-clear
A4	0.057±0.013	0.80±0.01	22.3±0.01	29±1	Not-clear
A5	0.031±0.001	0.17±0.03	18.07±0.02	13±2	Clear
A6	0.030±0.005	0.37±0.05	49.15±0.03	77±3	Clear

Table 6: Percentage cumulative drug release from the various formulation

Seconds	Percentage (CDR)			
	B1	B2	B3	B4
0	Nil	Nil	Nil	Nil
15	2.15±0.04	1.9±0.1	14.5±0.2	10.15±0.03
30	9.8±0.21	9.5±0.3	29.3±0.11	23.45±0.03
45	22.8±0.1	21.7±0.2	47.71±0.03	42.8±0.1
60	39.55±0.03	37.66±0.03	61.95±0.02	59.63±0.02
75	51.25±0.02	50.2±0.11	77.33±0.21	71.58±0.01
90	66.6±0.2	59.75±0.03	84.21±0.11	78.7±0.11
105	77.9±0.13	65±2	86.18±0.02	81.63±0.03
120	79.6±0.2	74.85±0.02	86.42±0.23	81.55±0.01

(paddle apparatus) with 300 ml of simulated salivary fluid (pH 6.8) as dissolution medium maintained at 37 ± 0.5°C. The medium was stirred at 100 rpm. Samples were withdrawn at every 30 s interval, replacing the same amount with the fresh medium [Table 4].[16]

RESULTS AND DISCUSSION

Evaluation of sublingual films

Table 5 shows the evaluation parameters of sublingual films.

Physical characterization of optimized formulations

It was observed that the uniformity of weight (0.027–0.051) and thickness (0.32–0.42 mm) was due to an increase in the concentration of polymer, due to which there will be an increase in the weight of the film and thickness. The observed disintegration time of the film contains in the range of 13.40–13.64. Folding endurance was found to be 71–77 which indicates that film has good flexibility. The tensile strength showed that an increase in the concentration of polymer of the prepared film was found to be 673.33–673.61 g/mm^2 that indicates the optimum temperature.

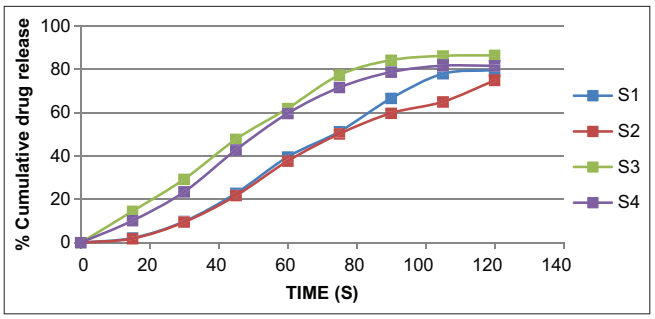

Figure 1: *In vitro* release studies of granisetron hydrochloride from sublingual film

Characterization of drug-loaded film

Table 6 shows the percentage cumulative drug release from various formulation.

In vitro dissolution study

It revealed that drug liberate from the formulation S3 was quicker than the B1, B2, and B4. The formulation-B3 had released about 86.18±0.02% of the loaded Granisetron Hydrochloride, while the formulations B1, B2 and in B4 released 79.6±0.2%, 74.85±0.02% and 81.63±0.03% of the drug, respectively [Figure 1].

SUMMARY

We prepared a fast-dissolving sublingual film for the first time by granisetron hydrochloride. The preparation exhibited outstanding stability of the granisetron hydrochloride. The fast-dissolving sublingual film of granisetron hydrochloride can be considered for cancer patients receiving chemotherapy or radiotherapy which may subsequently induce vomiting sensation. The characterisation studies had indicated quick release of the drug which may produce quick onset of action. Further, the method adopted for the preparation was simple and reproducible with minimum ingredients that makes the product more versatile.

CONCLUSION

It has been concluded that granisetron hydrochloride-loaded sublingual film was effectively formulated. Sublingual carrier system will help in achieving improved bioavailability by avoiding first-pass metabolism and improvement in patient conformity. Incorporation of sweetening agent Mannitol resulted in taste masking.

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