RESEARCH ARTICLE

Design and Evaluation of Formulated Mouth Dissolving Film of Domperidone and Study the Effect of Concentration of Polymers on Drug Release

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Abstract

Aim: One of the important aspects of medication, which are depending on the basis of drug release and bioavailability. Orally fast dissolving film is a new drug delivery system designed for the oral delivery of the drugs and developed on the basis of technology of the transdermal patch. **Materials and Methods:** Designed thin mouth dissolving film of domperidone with polyvinyl alcohol (PVA) as a water-soluble polymer and polyethylene glycol 400 as a plasticizer was prepared by solvent casting method. Fourier-transform infrared study was conducted for drug-polymer interaction and formulation. **Results and Discussion:** The designed films were evaluated for mechanical properties and *in vitro* dissolution test, including drug-polymer interaction study. Stability study was conducted for physical stability and *in vitro* drug release. **Conclusion:** It was observed that drug release was decreased as the concentration of polymer increases. The various parameters were studied such as the effect of concentration of PVA and effect of plasticizers on film properties. The high % drug release of the film in 6.8 pH phosphate buffer indicated that it could be helpful for the treatment of common cold, rhinitis, where quick bioavailability of drug is desired.

Key words: Fast dissolving films, oral mucosa, solvent casting, polyvinyl alcohol

INTRODUCTION

Omitting is the uncontrollable reflex that expels the contents of the stomach through the mouth. It is also called "being sick" or "throwing up." Domperidone is the choice of drug to treat nausea and omitting. The oral route is one of the most preferred routes of drug administration as it is more convenient, cost-effective, and ease of administration lead to high level of patient compliance. The oral mucosa is composed of an outermost layer of stratified squamous epithelium. Below this lies a basement membrane, a lamina propria followed by the submucosa as the innermost layer.[1] The external carotid artery is the main source of blood supply to the oral tissues. Saliva is essentially a protective fluid for the tissues of the oral cavity. The mucus film may act as a barrier, although unless the drugs bind specifically with the mucins or are large molecules.[2] Solvent casting is the most preferred method to manufacture fast dissolving film. In this method, initially, water-soluble ingredients are mixed in water to form viscous solution. Active pharmaceutical ingredients (API) and remaining ingredients are dissolved in smaller amount of solution and combined with bulk using high shear processor. Vacuum is used to remove the air entrapped. The solution formed is then cast as a film and pour the solution in a glass mold and allow the solution to dry in an oven at 45–50°C which is then cut into pieces of the desired size.[3]

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Silent feature of mouth dissolving film

- Thin elegant film.
- Available in various size and shapes.
- Unobstructive.
- Excellent mucoadhesion.
- Fast disintegration.
- Rapid release.[4]

The ideal characteristics of a drug to be selected

- The drug should have pleasant taste.
- The drugs with smaller and moderate molecular weight are preferable.
- The drug should have good stability and solubility in water as well as in saliva.
- It should be partially unionized at the pH of oral cavity.[5]

Advantages of orally fast dissolving film

- Oral dissolving films can be administered without water, anywhere, anytime. Due to the presence of larger surface area, films provide rapid disintegrating and dissolution in the oral cavity.
- Beneficial in cases such as motion sickness, acute pain, pseudo episodes of allergic attack, or coughing, where an ultrarapid onset of action required.
- Suitability for geriatric and pediatric patients, who experience difficulties in swallowing.
- The oral or buccal mucosa being highly vascularized, drugs can be absorbed directly and can enter the systemic circulation without undergoing first-pass hepatic metabolism. This advantage can be exploited in preparing products with improved oral bioavailability of molecules that undergo first pass effect.[6]

Disadvantages

- High doses cannot be incorporated.
- Dose uniformity is a technical challenge.
- Drug should have high oral bioavailability.
- Oral films have expensive packaging.[6]

MATERIALS AND METHODS

API – domperidone

Domperidone is the antiemetic activity and it is dopamine antagonist. The antiemetic properties of domperidone are related to its dopamine receptor blocking activity at both the chemoreceptor trigger zone and at the gastric level. Domperidone was obtained as a generous gift from Marksans Pharma LTD, Verna, Goa. The drug was stored in an amber glass container.[7]

Excipients

Polyvinyl alcohol (PVA)

PVA is the white granular powder which has the film forming property. PVA is the water-soluble polymer. PVA was kept in a well-closed container.[8] PVA obtained as the generous gift from Colorcon Asia Pvt. Ltd. Goa.

Polyethylene glycol (PEG) (400)

PEG 400 is the flexible water-soluble polymer. PEG is the lubricating coating for film surface in the aqueous as well as on non-aqueous environment.[9] PEG obtained as the generous gift from Colorcon Asia Pvt. Ltd. Goa.

Crospovidone

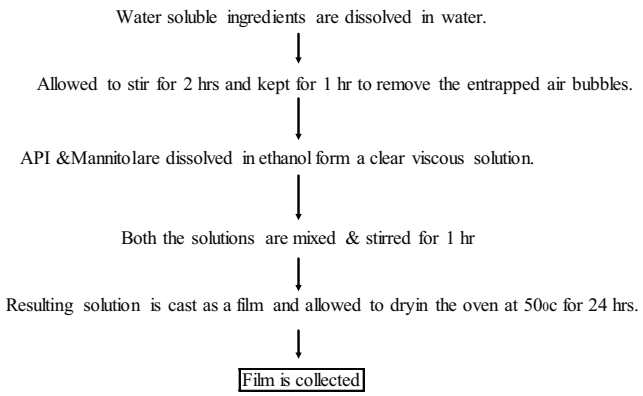
Crospovidone is one of the main superdisintegrants. Crospovidone is the pharmaceutical carrier to modify the solubility and dissolution of poorly water-soluble drugs.[10] Crospovidone obtained as the generous gift from Colorcon Asia Pvt. Ltd. Goa.

Mannitol

Mannitol is polyol (sugar alcohol). Mannitol is used as the sweetening agent. Mannitol and other chemicals were analytical grade.[11]

Method

Mouth dissolving film of domperidone was prepared by solvent casting method. Aqueous solution I was prepared by dissolving the polymer, crospovidone, and PEG 400 in specific proportion in distilled water and was allowed to stir for 2 h and kept for 1 h to remove the air bubbles entrapped. Aqueous solution II was prepared by dissolving the drug and mannitol in ethanol. Both aqueous I and II were mixed and stirred for 1 h. Then, mixture solution was casted into a Petridis and it was dried in the oven at 50°C for 24 h. The film was carefully removed from the Petridis, checked for any imperfections, and cut according to size required for testing (4*2 cm).[12]



Composition of mouth dissolving film

Composition of mouth dissolving film is given in the Table 1.

Evaluation of prepared mouth dissolving film

Morphological properties

Properties such as homogeneity, color, transparency, and surface of the oral films were evaluated by visually inspection. Results are reported in Table 2.

Visual appearance

The oral fast dissolving films were evaluated for their appearance as transparent or opaque. Results are reported in Figure 1.

Folding endurance

The folding endurance was measured manually for the prepared films. A film of film was repeatedly folded at the same place till it broken. Results are reported in Table 3.

Uniformity of content

The test for uniformity of content of preparations is based on the assay of the individual contents of active substance. Content uniformity is determined by estimating the API content in individual film. Limit of content uniformity is 85–115%. Due to intimate contact the mobility of drug particles in swollen matrices is decreased, which leads increase in disintegration time. Ultraviolet (UV) spectroscopy used for determines the contents of uniformity of Agilent Technologies Company. Results are reported in Table 4.

Disintegration test

Film is examined using disintegrating test apparatus (single unit). The disintegrating time was carried out in 900 ml phosphate buffer (pH 6.8). All determinations were performed in triplicate. Disintegration test apparatus was used to determine disintegration time of Indo Sati Company. Results are reported in Table 5.

Dissolution and in vitro drug release

1. Medium: Phosphate buffer pH 6.8.
2. Volume: 900 ml.
3. Apparatus: USP-Type II.
4. RPM: 50 rpm.
5. Time point: 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, and 120 s.
6. Volume withdrawn: 5 ml of solution.
7. Temperature: 37°C ± 0.5°C
8. λ maxima: 285 nm.

The dissolution study was conducted in 900 ml of phosphate buffer (pH 6.8) using paddle apparatus at 37°C ± 0.5°C and at 50 rpm. The dissolution test apparatus used for dissolution study was of Veego Company. Results are reported in Table 6 and Figure 2.

Stability study as per ICH guideline

The accelerated stability was checked by keeping the film at room temperature up to 30 and 60 days. Samples were evaluated for assay and drug release.[13,14] Results are reported in Tables 7 and 8 and Figures 3 and 4.

RESULT AND DISCUSSION

Drug authentication (domperidone)

Appearance and color

The powder sample was found to be colorless or white amorphous powder (B.P.)

Assay

The percentage purity of given obtained sample of domperidone was found to be 97.12% by assay method. Absorption maxima of domperidone in methanol as shown in Figure 5.

Melting point

The melting point was found between 244°C and 246°C. It indicates that the drug was in a pure form.

UV-visible spectroscopy of plain domperidone

The dissolved domperidone in 0.1N HCL showed an absorbance maximum (λ max) at 283 nm as shown in Figure 6.

Differential scanning calorimetry (DSC) study of domperidone

DSC thermogram of domperidone represented thermal events for melting endothermic peak at 249.97°C with the fusion enthalpy 5.44 J/g. The DSC for the study of domperidone was of Shimadzu, model DT30. DSC thermogram of domperidone given in the Figure 7.

Calibration curve of domperidone using UV spectrophotometer

The calibration curve of domperidone was prepared in buffer pH 0.1N HCL. The observation shows the various concentrations (ppm) of domperidone with their respective absorbance at λ max 283 nm and Figure 8 shows the calibration curve with regression coefficient 0.9954, slope 0.0594. The results indicated that there is a linear relationship between concentration and absorbance. Calibration curve statistics reported in the Table 9.

Table 1: Composition of mouth dissolving film

Ingredients	Batch No 01	Batch No 02	Batch No 03	Batch No 04	Use of Ingredients
Domperidone	20 mg	20 mg	20 mg	20 mg	API
PVA	100 mg	200 mg	300 mg	400 mg	Polymer
PEG 400	4 ml	4 ml	4 ml	4 ml	Plasticizer
Crospovidone	5 mg	5 mg	5 mg	5 mg	Superdisintegrants
Mannitol	70 mg	70 mg	70 mg	70 mg	Sweetening agents

Table 2: Morphology of prepared mouth dissolving film

Formulation	Surface
F1	Smooth, transparent
F2	Smooth, transparent
F3	Smooth, transparent
F4	Smooth, transparent

Table 3: Folding endurance of prepared mouth dissolving film

Formulation	Folding endurance
F1	>350
F2	>350
F3	>350
F4	>350

Compatibility study

Fourier-transform infrared (FTIR) spectroscopy

The FTIR spectra of pure domperidone and PVA physical mixture are shown in Figure 9. The IR spectrum of domperidone and PVA physical mixture shown characteristic peaks at N-H stretching at 3097 cm–, C = O stretching at 1714 cm^{-1}. The spectrum also shown, symmetric C-H stretching at 2786.1 cm^{-1}, N-H deformation at 1693 cm^{-1}, and C-N at 1492 cm^{-1}, these peaks seemed to be retained at almost the same wave number with the same intensity in the spectra of pure domperidone. Which signify the absence of any potential physical or chemical interaction between the drug and polymer. Hence, the polymer was found to be compatible with the drug. FTIR spectroscopy of Shimadzu, model FTIR-8400S.

Formulation and evaluation

Morphology

The morphology of all the formulation was found smooth and transparent, without any scratches and free from bubbles.

Visual appearance

The visual appearance of formulations was semitransparent because PEG 400 was used as a plasticizer. While films from all the formulations were free of bubble.

Folding endurance

Folding endurance is dependent on polymer and plasticizer concentration. The folding endurance was measured manually for the prepared films. The folding endurance for all the formulation was found more than 350 times which was satisfactory to reveal good film properties for all the formulation as shown in Table 5.

Table 4: % Drug contents of formulations

Formulation	% Drug contents
Formulation 1	110.8 ± 0.45
Formulation 2	96.58 ± 1.44
Formulation 3	91.60 ± 0.84
Formulation 4	86.34 ± 1.07

Content uniformity

The drug content results of all individual formulation are mentioned in Table 6. The average values of content uniformity were found to be in the range of 86.34% ± 1.07–110.8% ± 0.45. The result indicated that the process employed to prepare strips in this study was capable of producing strips with uniform drug content.

Disintegration time

The disintegration time of the fast dissolving films was found to be in the range of 11.66 ± 1.52–17.66 ± 1.52 s. It was observed that as the concentration of polymer in the strip increased, the disintegration time was increased. This might be due to increased level of polymer, results in the formation of high viscosity gel layer caused by more intimate contact between the particles of polymer. Due to intimate contact the mobility of drug particles in swollen matrices is decreased, which leads increase in disintegration time.

FTIR spectroscopy of formulation

FTIR spectra of formulation were characterized by N-H stretching at 3097 cm^{-1} and C = O stretching at 1714 cm^{-1}, for the presence of –CO-NH group. The spectrum also shows asymmetric C-H stretching at 2952 cm^{-1}, symmetric

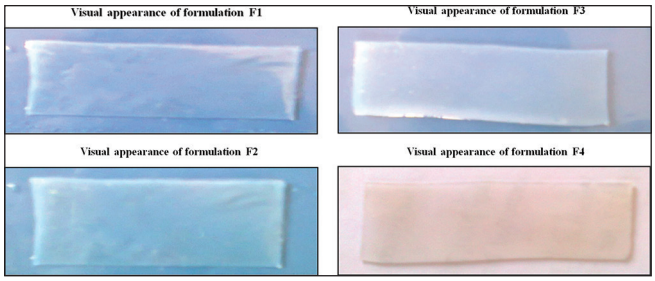


Figure 1: Visual appearance of formulations F1, F2, F3, F4

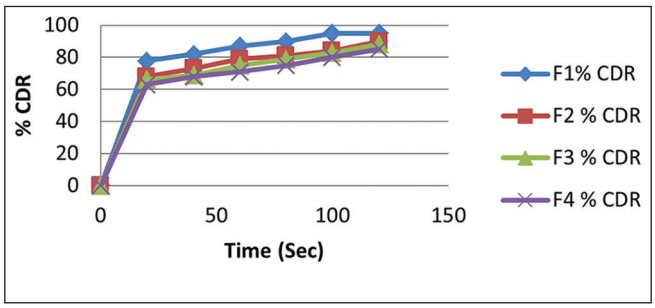


Figure 2: % Cumulative drug release versus time (sec) of prepared films

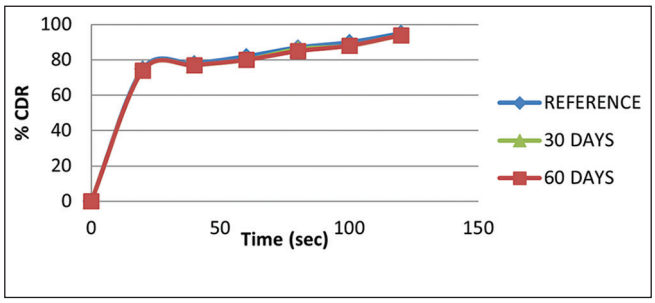


Figure 3: % Cumulative drug release of reference formulation F1 with stability study formulation F1

C-H stretching at 2786.1 cm^{-1}, N-H deformation at 1693 cm^{-1}, C = C at 1604 cm^{-1}, and C-N at 1492 cm^{-1}. These peaks seemed to be retained at almost the same wave number with the same intensity in the spectra of pure domperidone. Furthermore, no extra peak was observed in FTIR spectrum of formulations. Which indicate the absence of any potential physical or chemical interactions between the drug and polymer and other formulation additives. Hence, the formulation excipients were found to be compatible with drug fourier-transform infrared spectroscopy of formulation F1 shown in Figure 10.

In vitro drug release

Dissolution studies of all the batches were carried out in phosphate buffer (pH6.8) as a dissolution medium. Among the drug release studies of formulations F1–F4, the maximum drug release was found to be 95.67 ± 0.72% in formulation F1, whereas minimum amount of drug release was found to be 85.43 ± 0.49% in formulation F4. The % cumulative drug release (CDR) of all formulations of oral fast dissolving film of domperidone is given in Table 8.

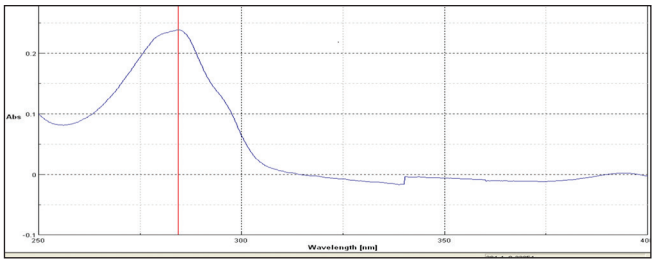


Figure 4: Absorption maxima of domperidone in methanol

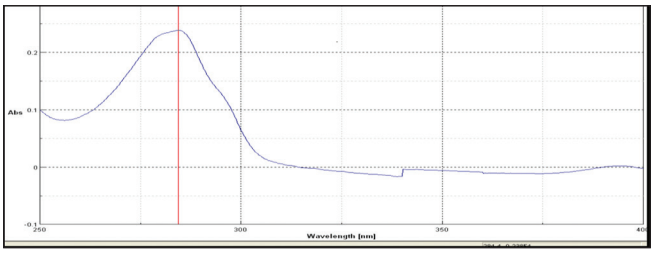


Figure 5: Absorption maxima of domperidone in methanol

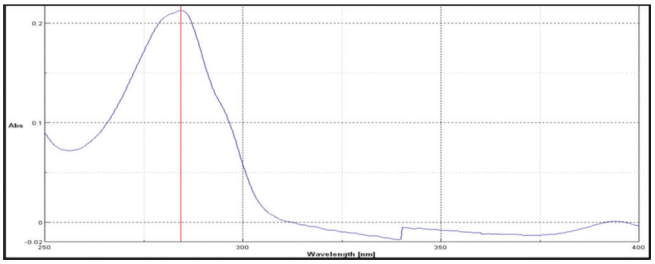


Figure 6: Absorption maxima of domperidone in 0.1N HCL

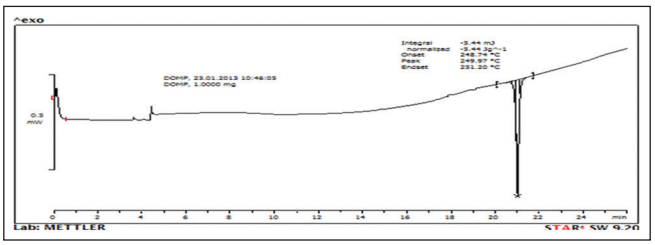


Figure 7: Differential scanning calorimetry thermogram of domperidone

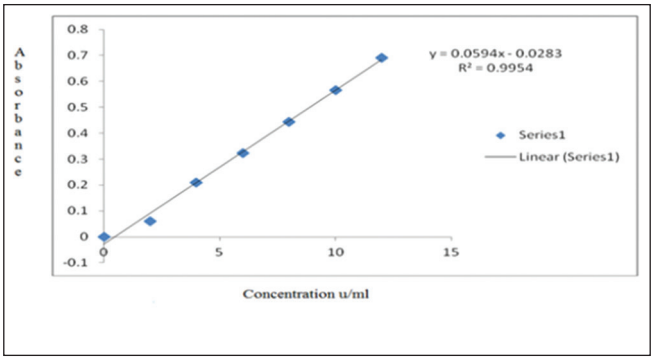


Figure 8: Calibration curve

Percentage (%) CDR

In vitro drug release studies were performed for all the prepared formulations using phosphate buffer pH 6.8 as a dissolution medium and measuring drug concentration by UV-visible spectrometer at 283.0 nm. The studies were performed up to 2 min. Distinguishable difference was observed in the release of domperidone-containing various concentrations of PVA. The graph was plotted by taking CDR versus time (sec) and graph was shown in Figure 2.

Comparing the dissolution profile of formulation F1, F2, F3, and F4, when the PEG 400 concentration kept constant (4 ml) and PVA concentration increased from F1 100 mg, F2 200 mg, F3 300 mg, and F4 400 mg, the observed percent drug release was in the order of F1>F2>F3>F4. After 2 min, the release was found to be 95.67>90.99>88.11>85.43 for F1>F2>F3>F4, respectively, films. In the above films, the percentage of PVA increased which slower the release of drug from the films. Due to increased level of polymer, results in the formation of high viscosity gel layer caused by more intimate contact between the particles of polymer. Due

Table 5: Disintegration time of formulations

Formulation	Disintegration time (s)
F1	11.66±1.52
F2	12.33±0.57
F3	14.33±2.08
F4	17.66±1.52

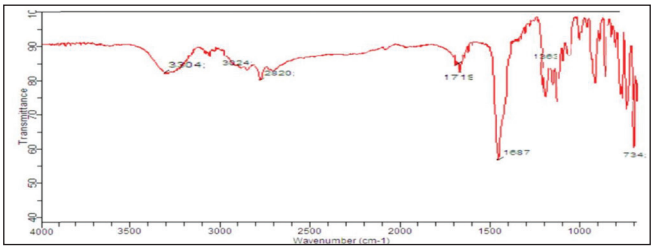


Figure 9: Fourier-transform infrared spectroscopy of physical mixture of domperidone and polymer

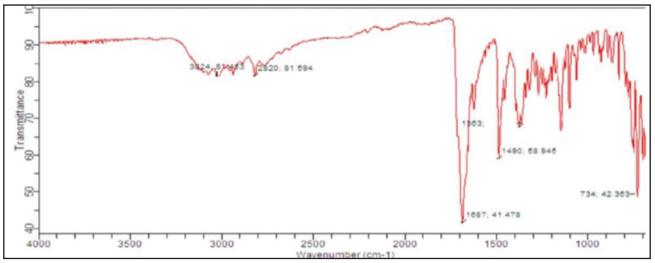


Figure 10: Fourier-transform infrared spectroscopy of formulation F1

Table 6: % CDR of prepared film

Time seconds	F1%CDR	F2%CDR	F3%CDR	F4%CDR	Average %CDR
0	0.00	0.00	0.00	0.00	0.00
10	73.44±0.45	67.95±0.45	65.16±0.78	60.57±0.95	67.32
20	75.78±0.87	68.58±0.78	66.96±0.39	63.00±0.39	69.12
30	77.22±0.10	71.28±0.63	67.77±0.10	65.25±0.10	71.25
40	78.84±0.98	73.80±0.92	69.93±0.205	68.31±0.82	73.65
50	80.19±0.93	75.60±0.51	72.99±0.98	69.66±0.78	75.15
60	82.80±0.54	79.02±0.10	75.15±0.56	71.19±0.62	77.67
70	84.78±0.89	79.74±0.67	76.86±0.72	73.89±0.60	79.47
80	87.93±0.90	81.72±0.89	79.92±0.10	75.15±0.37	81.60
90	89.46±0.10	83.07±0.69	81.72±0.61	77.58±0.74	83.37
100	90.36±0.75	84.60±0.73	83.25±0.69	80.46±0.107	85.14
110	92.70±0.69	89.10±0.106	84.87±0.38	81.90±0.93	87.90
120	95.67±0.72	90.99±0.83	88.11±0.48	85.43±0.49	90.03

CDR: Cumulative drug release

Table 7: Stability study for visual appearance and weight variation of prepared films

S. No	Visual appearance			
	F1	F2	F3	F4
0 day	Transparent	Transparent	Transparent	Transparent
30 days	Transparent	Transparent	Transparent	Transparent
60 days	Transparent	Transparent	Transparent	Transparent

Table 8: % drug release of formulation F1 after stability study

Time (sec)	% cumulative drug release of formulation F1 after stability		
	0 day (Reference)	30 days	60 days
20	75.78±0.87	74.56±0.90	74.47±0.103
40	78.84±0.98	77.67±0.65	77.53±0.56
60	82.80±0.54	80.98±0.95	80.90±0.076
80	87.93±0.90	86.89±0.39	85.43±0.34
100	90.36±0.75	88.78±0.50	88.90±0.84
120	95.67±0.72	94.78±0.43	94.28±0.54

Table 9: Calibration curve statistics

Parameters	Observations
Absorbance maxima	283
slope	0.0594
Intercept	0.0283
Coefficient of correlation	0.9954

to which the mobility of drug particles in swollen matrices is decreased, which leads increase in disintegration time.

Stability study

Stability study of mouth dissolving film of domperidone for the physical parameters

The optimized formulation F1 was withdrawn at the end of 30 and 60 days and evaluated for the physical parameters. The observations of stability studies of optimized formulation F1 are shown in Table 9. The stability studies of the optimized formulation F1 revealed that no significant changes in the physical parameters were observed at the end of 30 and 60 days. However, storage at room temperature and moisture proof packaging are essential to ensure stability of this type of formulation.

In vitro drug release after stability study

The optimized formulation F1 was withdrawn at the end of 30 and 60 days and evaluated for %CDR. Comparison of drug release profile of reference (F1 before stability study) and test (F1 after 30 and 60 days stability study) as shown in Figure 3. The difference factor (F1) value was found to be 0.50 and 0.59. Form the results of stability study of optimized formulation F1 revealed that non-significant changes in the %CDR after 30 and 60 days.

Assay

The percentage purity of given obtained sample of domperidone film F1 was found to be 95.10% for stability study by reported assay method. There was no significant change in purity of domperidone. Absorption maxima of domperidone in methanol are shown in Figure 4.

CONCLUSION

A novel dosage form of fast dissolving films for oral cavity was developed and evaluated. The various parameters were studied such as the effect of concentration of PVA and effect of plasticizers on film properties. FTIR studies confirmed that excipients are compatible with drug. The PVA-based fast dissolving strip of domperidone obtained by the solvent casting method showed acceptable mechanical characteristics and satisfactory % drug release in formulation F1. The prepared film was transparent with smooth surface without any interactions between drug and polymer. The high % drug release of the film in 6.8 pH phosphate buffer indicated that it could be helpful for the treatment of common cold, rhinitis, where quick bioavailability of drug is desired.

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