# DEVELOPMENT AND EVALUATION OF DOMPERIDONE ORAL FILM USING MIXED SOLVENCY CONCEPT

**Kirti Tomer[a]*, Amit Kumar Jain[a] and Neha Gehlot[a]**

(Received 12 March 2021) (Accepted 26 March 2024)

**ABSTRACT**

This study aimed to develop and evaluate oral film of antiemetic drug-using mixed solvency concept. The mixed-solvency concept was used in the solubility enhancement of domperidone, an antiemetic drug that is practically insoluble in water. Different types of solubilizers have been used for solubility improvement of domperidone and poly ethylene glycol, niacinamide, caffeine were found to be effective. Five formulations were prepared by using HPMC E15 a film-forming polymer. The prepared oral films were subjected to evaluation for thickness, pH, drug content, folding endurance, stability and *in vitro* drug release profile. The % *in vitro* drug release of the best two formulations F3 and F5 were 90.70% and 96.62 % respectively. From the above study, it was concluded that the solubility of the practically insoluble drug, domperidone could be improved successfully by using different water-soluble solubilizers in different ratios under the mixed-solvency concept.

**Keywords:** Oral film, PEG-Polyethyleneglycol, mixed-solvency, HPMC E15

## ABBREVIATIONS

HPMC-Hydroxypropylmethylcellulose; PEG-Polyethylene glycol; CAF- Caffeine; HPMC- Hydroxy propyl methyl cellulose; SC- Sodium Caprylate; PG- Propylene glycol; W- Drug-Excipient combination; CYCLO- Cyclodextrin; NM- Niacinamide

## INTRODUCTION

Nausea and vomiting are not diseases, but they are only indications of changed physiological functions. Treatment depends on the diagnosis of the underlying disorder, which might not include drugs[1]. The action of vomiting is usually produced with the aid of a sequence of coordinated modifications in GI activity with forceful contractions of the stomach pylorus; and rest of the fundus, cardiac sphincter, and esophagus[2-3]. These with forceful contractions are generally initiated by chemoreceptor trigger zone (CTZ), in response to chemical stimuli. The vomiting center (VC) in the brain initiates the emetic reaction which triggers the act of vomiting[4,5].

The vomiting center has many excitatory inputs from nerve endings of vagal sensory nerves in the gastrointestinal area, labyrinths through the vestibular nuclei, controlling centers in the cortex (while vomiting is produced with the aid of unfavourable experience or in anticipation of such incidences), CTZ and intracranial strain receptors[6].

The goal of the novel drug transport system is to deliver a specific amount of drug to the right site within the body to achieve quickly and then maintain the specified drug concentration. There are many benefits to this system, though there are few factors that limit its usage.

An oral rapid drug dissolving system is a standard approach to increase patient compliance, by utilizing its fast absorption and self-management without swallow and chewing[7,8]. The oral quick-dissolving film is a unique technique for drug release in which thin film is designed by way of the usage of hydrophilic polymers, which rapidly dissolve inside the oral cavity[9]. The film can eliminate the problem of patient inconvenience. A perfect film should encompass properties like the pleasing taste, high firmness, ease of usage and administration, and no water needed for the application[10]. A fast-dissolving film is a film that dissolves or disintegrates in the oral cavity without the need for water or chewing[11]. Oral films are a unique and ideally accepted dosage form by consumers[12-13]. But, due to the poorly soluble antiemetic drug, the bioavailability problem has to be overcome by using different types of strategies for solubility enhancement[14].

[a] Department of Pharmaceutics, Faculty of Pharmacy, B.R. Nahata College of Pharmacy, Mandsaur University, Mandsaur – 458 001, Madhya Pradesh, India

*For Correspondence: E-mail: kirtitomarmip@gmail.com

https://doi.org/10.53879/id.61.04.12929

### Mixed solvency concept

Each and every single substance existing in the world which includes gases, liquids and solids has solubilizing capability; this concept was used by Dr. R. K. Maheshwari[15]. According to his concept, each matter is a solubilizer[16]. As per his statement, the dissolution of water-soluble substances in water or aqueous vehicle must serve as a good solvent, especially for those substances which are insoluble or poorly soluble in water[17]. Since a single solubilizing agent may be toxic for living organisms and patients, therefore, we can use a lesser quantity of various solubilizers in a single formulation in order to overcome the problem of toxicity of a single solubilizer. Less amount of solvent may assure the safety of dosage form, and expected solubility can be achieved[18].

## MATERIALS AND METHODS

### Materials

Domperidone was obtained as a gift sample from Asoj Soft Caps Pvt. Ltd., Vadodara, Gujarat. Excipients were obtained from B. R. Nahata College of Pharmacy, Mandsaur, MP.

## DRUG CHARACTERIZATION

### UV Spectrophotometric analysis

10 µg $mL^{-1}$ solution of domperidone (DOM) was scanned using a UV/visible spectrophotometer (Shimadzu- 1700) over 200-400 nm range. The UV spectrum of the domperidone is represented in Fig. 1.

### Infrared study

IR spectrum of domperidone was recorded on an FTIR spectrophotometer Shimadzu Japan Model No. 2800 in the region of 450-4000 $cm^{-1}$ and represented in Fig. 2.

### DSC study

Accurately weighed drug sample of 3 mg was placed in a small sealed aluminum pan (DSC Cell), then subjected to heating with nitrogen flow at the rate of 40 mL $min^{-1}$ at 30-300 °C and a scanning rate of 100°C per min. An empty aluminum pan was placed on the left side. DSC spectrum of the domperidone is represented in Fig. 3.

### Drug-excipients physical compatibility study

The physical compatibility study was performed by keeping the drug in contact with various formulation excipients. Samples were placed in the vials at room temperature and refrigerated condition (2-8°C) for 30 days and they were checked after every week, throughout the month. The results are given in Table II.

### Determination of solubility

Solubility of drug was tested in demineralised water and phosphate buffer (6.8), as shown in Table III.

## FORMULATION DEVELOPMENT

### Preparation of solubilizers in aqueous solution

For the selection of solubilizers, different concentrations of hydrophilic chemicals and plasticizers were used such as caffeine, sodium citrate, niacinamide, β-cyclodextrin, propylene glycol, PEG 400, PEG 600, glycerin and PVP K25. The overall solute concentration in the prepared solution was kept at ≤ 30% w/V concentration and the percentage solubility of the domperidone was determined, which is depicted in Table IV.

### Polymer selection

Based on solubility enhancement of domperidone in different concentrations of individual solubilizers and their combinations, two best blends of solubilizers were selected, with blend compositions NM: PEG400: CAF =5:15:5 (B1) and NM: PEG600: CAF = 5:15:5(B2), for further studies.

### Preparation of solo film

Into a 10 mL vial, 0.85 mL of selected solubilizer blend was poured. To this, accurately weighed 10 mg drug was added, and the vial was capped with rubber closure. The contents of the vial were shaken for proper drug solubilization in blend. Then, 0.15 mL plasticizer and 60 mg polymer were added, to the vial, and it was

**Table I: Optimized blend for formulation development**

| Film batch | F1 | F2 | F3 | F4 | F5 |
|---|---|---|---|---|---|
| Blend (8.5mL) | B1 | B1 | B1 | B2 | B2 |
| HPMC E15 | 5.0 %w/V | 5.2 %w/V | 5.5 %w/V | 5.8 %w/V | 6.0 %w/V |
| PEG600 | 15 %V/V | 15 %V/V | 15 %V/V | 15 %V/V | 15 %V/V |
| The drug used for 10 mL film solution | 400 mg | 400 mg | 400 mg | 400 mg | 400 mg |

**Table II: Drug-excipient physical compatibility studies**

| Sr. No. | Drug- excipient (1:1) | Initial description | Room temperature (25±2$^0$C) | | | | Refrigerated (2-8°C) | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | W 1 | W 2 | W 3 | W 4 | W 1 | W 2 | W 3 | W 4 |
| 1 | DOM | White powder | NC | NC | NC | NC | NC | NC | NC | NC |
| 2 | DOM + NM | White powder | NC | NC | NC | NC | NC | NC | NC | NC |
| 3 | DOM + SC | White powder | NC | NC | NC | NC | NC | NC | NC | NC |
| 4 | DOM+ PVPK25 | Creamy powder | NC | NC | NC | NC | NC | NC | NC | NC |
| 5 | DOM + PG | White liquid (suspension) | NC | NC | NC | NC | NC | NC | NC | NC |
| 6 | DOM + GLY | White liquid (suspension) | NC | NC | NC | NC | NC | NC | NC | NC |
| 7 | DOM +CF | White powder | NC | NC | NC | NC | NC | NC | NC | NC |
| 8 | DOM + UR | Light yellow powder | NC | NC | NC | NC | NC | NC | NC | NC |
| 9 | DOM + HPMCE15 | White powder | NC | NC | NC | NC | NC | NC | NC | NC |

DOM = domperidone, NM = niacinamide, SC = sodium caprylate, PG = propylene glycol, GLY = glycerin, UR = urea, CF = caffeine, NC = no change, W = drug-excipient combination

placed on mechanical shaker for uniform mixing. The removal of entrapped air from the prepared solution was done by keeping the solution undisturbed for 3 h. Finally, the viscous solution obtained after swelling of polymer was spread over a glass plate, and it was dried at room temperature for 24h.

## EVALUATION OF THE CASTED POLYMERIC FILM

### Folding endurance

The folding endurance value of the film was determined by counting the number of times the film was folded though the same point without breaking.

### Thickness

Film thickness was determined by using a micrometer (screw gauge) as the mean thickness of 5 locations (center and 04 corners)[20].

### Optimization of polymer concentration

The selected polymer (HPMC E-15) with different concentrations was incorporated in films, and their different properties were observed, as indicated in Table V.

### Selection of plasticizer

Taking HPMC E-15 as polymer with different plasticizers concentrations (15% V/V) films were formulated and their different properties were observed as indicated in Table VI.

### Optimization of plasticizer concentration

HPMC E-15 and plasticizer (PEG 600) with different concentrations (10% V/V – 20% V/V) were incorporated in films, respectively, and their film properties were studied and are tabulated in Table VI.

### Optimized film batches

Based on previous studies, five batches were selected for further optimization (Table I).

### Method of preparation of fast dissolving film

Accurately weighed 400mg domperidone was taken in a 10mL vial containing 8.5mL of respective solubilizer blend. Then, the mixture was shaken vigorously, different concentration of HPMC E-15 (optimized polymer), and respective concentration of PEG 600 (optimized plasticizer) were added into various prepared blends with drug and mixed uniformly using a glass rod. The preparations were kept undisturbed for 3h, so that the polymer could swell up properly, and, then 5mL of this solution was taken out with a pipette, and carefully poured over a rectangular base of the glass, and, then placed at an undisturbed place for proper drying at room temperature. Then, the films were cut into the dimension i.e. 2×2 cm$^2$ containing 10mg of domperidone. The prepared films were sealed in butter paper and polybags covering and were evaluated[19] .

## EVALUATION PARAMETERS

### *In vitro* dissolution study

This study was performed by using USP II dissolution apparatus using simulated saliva fluid as dissolution medium at 60 rpm, and keeping the temperature as

37±0.5 °C. At regular time intervals, samples (10 mL) were withdrawn and were analyzed spectrophotometrically at 282 nm after appropriate dilution with simulated saliva fluid. After each withdrawal, dissolution media was replaced with fresh simulated saliva fluid[20]. The results are reported in Table VIII.

### Drug content

In this study, a single domperidone film was taken in a 500 mL volumetric flask, and then the volume was made up to 500 mL with demineralized water. The absorbance of this solution was noted at 282 nm, and from these observations the concentration of the drug in the film and % drug content for 10 mg/2 $cm^2$ were calculated, as shown in Table IX.

$$\% \text{ Drug content} = \frac{\text{(practical value)}}{\text{(theoretical value)}} \times 100$$

### pH of film

The prepared oral film was dipped in10 mL water in a beaker. After 5 minutes, its pH was determined by pH electrode, as indicated in Table VII.

### Disintegration test

In a beaker, 25 mL of distilled water was poured and then, the film was placed under applied constant swirling motion. The time was noted when the film got completely disintegrated. The disintegration time is given in Table VII.

### Folding endurance

The number of foldings till the film breaks, was noted as folding endurance of film and the results are mentioned in Table VII.

### Thickness

The thickness of the film was measured at 5 different positions and the average values are mentioned in Table VII.

### Stability study of optimized batches F3 and F5

This study was carried out by storing the films at 25°C±2°C (in desiccators) and at 2-8 °C (in refrigerator) for period of 70 days, and then their drug content was determined. The result are tabulated in Table IX.

## RESULTS AND DISCUSSION

### Drug characterization

UV spectrum of domperidone obtained at 282 nm was found to be identical to that reported in the literature Fig. 1.

### Infrared study of domperidone

Domperidone FTIR spectrum (Fig. 2) was similar to the spectra reported in the literature.

### DSC study of domperidone

Domperidone DSC spectrum (Fig. 3) was similar to that reported in the literature.

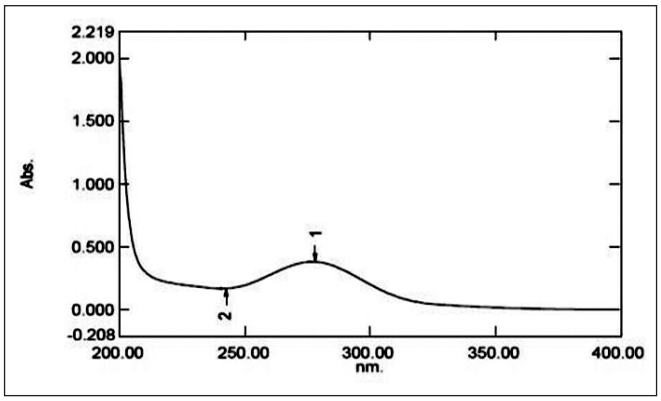


**Fig. 1: UV spectrum of domperidone**

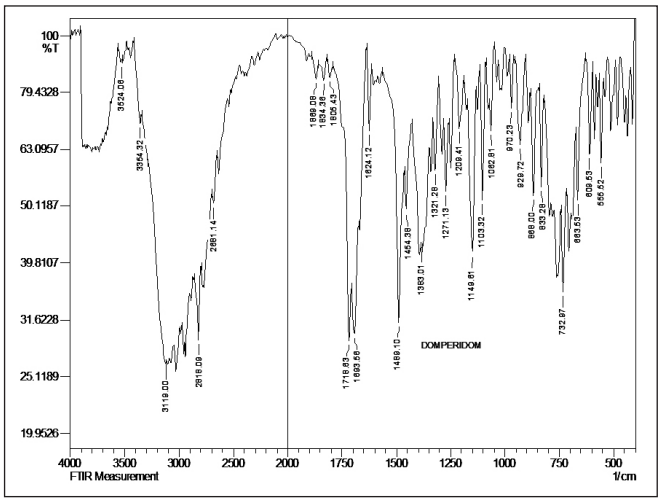


**Fig. 2: FTIR spectrum of domperidone**

**Table III: Solubility of domperidone**

| Solvent system | DM water | Phosphate buffer (pH 6.8) |
|---|---|---|
| Solubility (mg $mL^{-1}$) | 0.09 | 0.40 |
| Inference | Poorly soluble | Slightly soluble |

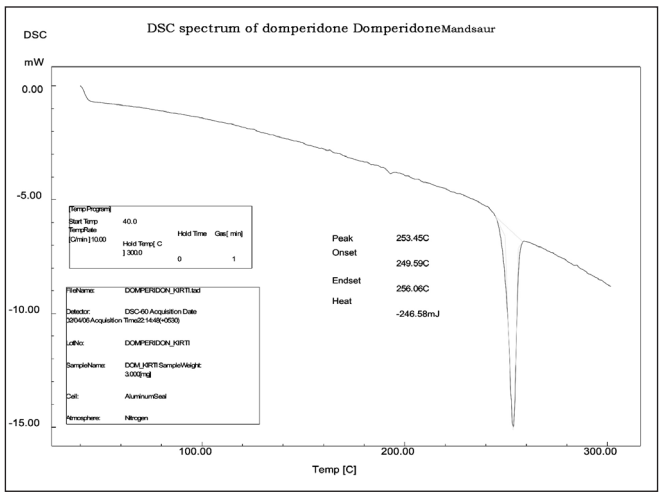


**Fig. 3: DSC spectrum of domperidone**

**Table IV: Drug solubility in various solubilizer blends**

| Sr. No. | Solubilizer blend | Solubilizer concentration (%w/V) | Solubility (mg $mL^{-1}$) | Solubility enhancement ratio |
|---|---|---|---|---|
| 1 | Demineralised water | --- | 0.0925 | --- |
| 2 | Propylene glycol | 15 | 0.0043 | 0.0464 |
| | | 20 | 0.0001 | 0.0010 |
| 3 | Glycerin | 15 | 0.0004 | 0.0043 |
| | | 20 | 0.0003 | 0.0032 |
| 4 | PEG 400 | 15 | 0.0002 | 0.0021 |
| 5 | PEG 600 | 15 | 0.0035 | 0.0378 |
| 6 | PVP K25 | 5 | 0.0249 | 0.2691 |
| 7 | Urea | 2 | 1.9769 | 21.37 |
| 8 | Caffeine | 5 | 2.8796 | 31.12 |
| 9 | Niacinamide | 5 | 2.4578 | 26.57 |
| 10 | Sodium caprylate | 5 | 0.0037 | 0.04 |
| 11 | Cyclodextrin | 5 | 0.0075 | 0.081 |
| 12 | Vanillin | 1 | 1.3248 | 14.32 |
| 13 | PEG400: CAF | 20:2 | 1.84 | 19.96 |
| 14 | GLY: CAF | 20:2 | 1.78 | 19.27 |
| 15 | CYCLO: CAF | 20:2 | 1.79 | 19.43 |
| 16 | PEG600: CAF | 20:2 | 1.87 | 20.23 |
| 17 | UR: CAF | 2:2 | 1.53 | 16.64 |
| 18 | PG: CAF | 20:2 | 1.74 | 18.82 |
| 19 | NM: CAF | 2:2 | 3.13 | 33.86 |
| 20 | CAFF: SC | 2:2 | 0.81 | 8.79 |
| 21 | PVPK25: CAF | 2:2 | 2.49 | 26.95 |
| 22 | CAF: NM | 5:5 | 13.75 | 148.75 |
| 23 | NM: PEG400: CAF | 2:15:2 | 5.19 | 56.11 |
| 24 | NM: PEG600: CAF | 2:15:2 | 8.92 | 96.21 |
| 25 | NM: PEG400: CAF | 5:15:5 | 78.26 | 846.05 |
| 26 | NM: PEG600: CAF | 5:15:5 | 85.42 | 923.45 |

*HPMC- Hydroxypropyl methylcellulose, CMC-Carboxymethyl cellulose*

## Optimization of plasticizer concentration

Based on film properties, 15% V/V concentration of PEG 600 was optimized, and results are given in Table VI.

**Table V: Properties of different concentrations of HPMC E-15**

| Polymer | Solubilizer blend | Property of film | | |
|---|---|---|---|---|
| | | Pourability | Appearance | Thickness |
| HPMC E15 (6%) | B1 | Pourable | Translucent | 0.05 mm |
| | B2 | Easily pourable | Transparent | 0.01 mm |
| HPMC E15 (7%) | B1 | Slightly difficult | Hazy | 0.09 mm |
| | B2 | Slightly difficult | Hazy | 0.09 mm |
| HPMC E15 (7.5%) | B1 | Very difficult to pour from vial | Translucent | Whole solution was not incorporated in film |
| | B2 | Non –pourable (Stuck inside vial) | ---- | |

**Table VI: Properties of film in presence of different concentrations of PEG 600**

| Plasticizer concentration | | 10% V/V | 15%V/V | 20%V/V |
|---|---|---|---|---|
| Appearance | B1 | Hazy | Translucent | Transparent |
| | B2 | Hazy | Translucent | Transparent |
| Thickness (mm) | B1 | 0.1 | 0.08 | 0.4 |
| | B2 | 0.12 | 0.09 | 0.2 |
| Folding endurance | B1 | 174 | 220 | 186 |
| | B2 | 182 | 226 | 188 |

## Evaluation of formulated film batches

Based on evaluation parameters of different batches of films, batches F3 and F5 gave better results, and were chosen as optimized batches, for further evaluation as reported in Table VII.

**Table VII: Evaluation of formulated film batches**

| Batch | F1 | F2 | F3 | F4 | F5 |
|---|---|---|---|---|---|
| Thickness (Average of 5 different positions) | 0.19 mm | 0.15 mm | 0.09 mm | 0.21 mm | 0.11 mm |
| Folding endurance (number) | 152 | 135 | 174 | 169 | 182 |
| pH | 6.9 | 6.85 | 6.83 | 6.89 | 6.81 |
| Disintegration time (sec) | 58 | 63 | 50 | 74 | 54 |

## Dissolution profile of batches F3 and F5

For optimized batches F3 and F5, the cumulative% drug release in simulated salivary fluid were found to be 90.70% and 96.62%, respectively (Fig. 4).

**Table VIII: *In vitro* dissolution profile**

| Sr. No. | Time (min/sec) | Cumulative % drug release | | | | |
|---|---|---|---|---|---|---|
| | | F1 | F2 | F3 | F4 | F5 |
| 1. | 30sec | 32.82 | 20.55 | 43.95 | 22.65 | 39.75 |
| 2. | 45sec | 48.96 | 33.52 | 50.79 | 28.47 | 45.33 |
| 3. | 1min | 53.72 | 62.33 | 67.52 | 29.88 | 55.67 |
| 4. | 2min | 62.98 | 66.32 | 80.72 | 34.28 | 70.85 |
| 5. | 5min | 70.63 | 67.22 | 92.47 | 48.82 | 78.95 |
| 6. | 10min | 74.88 | 67.85 | 98.68 | 73.81 | 88.25 |
| 7. | 15min | 74.96 | 68.33 | 99.13 | 85.81 | 92.65 |
| 8. | 30min | 85.62 | 68.52 | 99.57 | 93.47 | 92.87 |
| 9. | 45min | 89.33 | 70.58 | 99.62 | 94.56 | 93.99 |
| 10. | 60min | 89.68 | 67.99 | 99.70 | 88.71 | 96.62 |

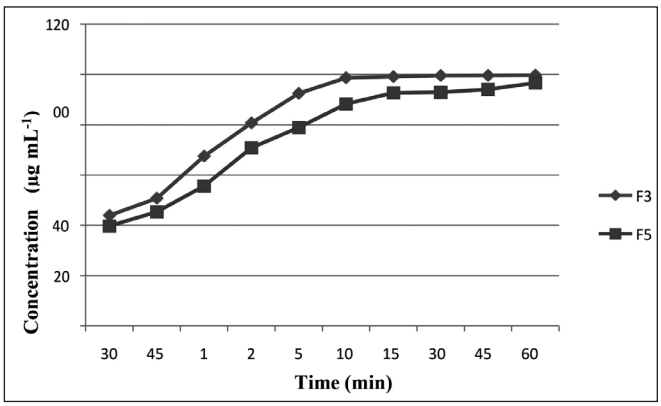


**Fig. 4: *In vitro* dissolution profile of optimized batches F3 and F5**

### Stability study of optimized batches F3 and F5

The stability studies of optimized batches showed that the domperidone films were stable at 25°C±2 °C as well as at 2-8 °C. The results reported in Table IX.

The characterization of domperidone drug sample has been done by FTIR spectroscopy, U.V. spectrophotometer and differential scanning calorimeter. The physical compatibility studies of drug and excipients were also included. The results of drug sample were similar to those reported in the literature. According to the pH of saliva, the phosphate buffer pH 6.8 was used in the preparation of the calibration curve of the drug sample.

**Table IX: Stability studies of final optimized batches F3 and F5**

| Stability condition | Sampling interval | % Drug content (10 mg/ 2 cm$^2$) | | pH | |
|---|---|---|---|---|---|
| | Days | Batch F3 | Batch F5 | Batch F3 | Batch F5 |
| 25 °C±2 °C | 0 | 99.78 | 99.82 | 6.80 | 6.80 |
| | 7 | 99.43 | 99.08 | 6.80 | 6.80 |
| | 14 | 98.73 | 98.46 | 6.82 | 6.81 |
| | 21 | 98.38 | 98.32 | 6.83 | 6.83 |
| | 28 | 98.04 | 98.04 | 6.85 | 6.83 |
| | 35 | 97.69 | 97.63 | 6.87 | 6.84 |
| | 42 | 97.34 | 96.99 | 6.88 | 6.85 |
| | 49 | 96.64 | 96.64 | 6.88 | 6.88 |
| | 56 | 96.30 | 95.99 | 6.90 | 6.90 |
| | 63 | 95.95 | 95.25 | 6.91 | 6.91 |
| | 70 | 95.56 | 94.90 | 6.93 | 6.92 |
| 2-8 °C | 0 | 99.47 | 99.43 | 6.80 | 6.80 |
| | 7 | 98.32 | 98.73 | 6.80 | 6.80 |
| | 14 | 98.38 | 98.38 | 6.80 | 6.81 |
| | 21 | 97.69 | 98.21 | 6.81 | 6.83 |
| | 28 | 97.34 | 97.63 | 6.82 | 6.85 |
| | 35 | 96.99 | 96.69 | 6.85 | 6.87 |
| | 42 | 96.64 | 96.32 | 6.88 | 6.88 |
| | 45 | 95.95 | 96.28 | 6.89 | 6.88 |
| | 56 | 95.56 | 95.76 | 6.89 | 6.90 |
| | 63 | 94.90 | 95.56 | 6.90 | 6.93 |
| | 70 | 94.56 | 94.54 | 6.91 | 6.96 |

The linearity of the curve showed that Beer Lambert's law was followed within the concentration range of 10-50 µg $mL^{-1}$ at 282nm. The aqueous solubility of the drug was found to be 0.0925 mg $mL^{-1}$. Different combinations of drug- excipient physical compatibility study were done, observing any physical changes in the blends of drug and excipient visually for one month. For enhancing the solubility of domperidone, solubility studies were performed at room temperature in different combination containing individual solubilizer or in a blend. The solubility of domperidone could be increased up to 8.54% (V/V) in an aqueous blend of solubilizers (5% w/V niacinamide+ 15% w/v polyethylene glycol+ 5% w/V caffeine), which was found to be the best among all combinations.

## CONCLUSION

The objective of this research work was to enhance the solubility of domperidone drug, which is practically insoluble in water. Physiologically compatible solubilizers were used to improve its solubility. The blends of solubilizers of total strength ≤ 30% w/V were used in selected final blends to get sufficient solubility. The best solubility enhancement ratio was observed in the combinations of solubilizers containing niacinamide, polyethylene glycol and caffeine. Film-forming polymers and plasticizers were screened for preparing oral film of domperidone. They were selected and optimized based on their physical properties, pH and disintegration time. Finally, five optimized batches of prepared films with 10mg of domperidone in 2×2$cm^2$ area, were formulated and their physical characteristics such as appearance, flexibility (folding endurance), thickness, pH, time for disintegration, and *in vitro* dissolution were studied.

After screening of film excipients, film development and evaluation of properties, F3 and F5 batches showed better *in vitro* dissolution profile, disintegration time and physical characters. Also, batches F3 and F5 were found to be stable for 70 days. The result of the above work indicate that the approach of the mixed solvency concept is safe, novel, user friendly and economical.

## REFERENCES


1. Andrew PL.R., Rapeport W.G and Sanger G.J.: Neuropharmacology of emesis induced by anticancer therapy. **Trends Pharmacol. Sci.**, 1988, 9(1), 334-341.
2. Barone J.A.: Domperidone: A Peripherally Acting Dopamine2-Receptor Antagonist, **The Ann Pharmacother.**, 1999, 33(1), 429-440.
3. Marty M.,Pouillart P., Scholl S., Droz J.P., Azab M., Brion N., Pujade-Lauraine E., Paule B., Paes D. and Bons J.: Comparison of the 5-hydroxytryptamine 3 (serotonin) antagonist ondansetron (GR 38032F) with high-dose metoclopramide in the control of cisplatin-induced emesis, **New. Engl. J. Med.,** 1990, 322(1), 816-821.
4. Board T., R. Ph. Board R. and R.N.: The Role of 5-HT3 Receptor antagonists in preventing postoperative nausea and vomiting, **AORN J.**, 2006, 83(1), 299-220.
5. Borison H.L., Borison R., Lawrence B.A. and Mccarthy N.H.: Phylogenic and neurologic aspects of the vomiting process, **J Clin. Pharmacol.**, 1981, 21(23), S2-S9.
6. Robbins N., Ito H., Melvin H., Scheinman M. and Peter J.G.: Safety of domperidone in treating nausea associated with dihydroergotamine infusion and headache, **Neurology**, 2016, 87(1), 1-5.
7. Muhammad Bilal H.M., Tehseen R., Muhammad J., Irfan B. and Saqib Z.: Oral Films: A Comprehensive Review, **Pak. J. Pharm.,** 2016, 5(12), 111-117.
8. Pallavi P. and Shrivastava S.K.: Fast dissolving oral films: An innovative drug delivery system, **Int. J. Sci. Res.**, 2014, 3(7), 2088.
9. Choudhary D.R., Patel V., Patel H., and Kundawala A.J.: Exploration of film-forming properties of film formers used in the formulation of rapid dissolving films, **Int. J. Chemtech. Res.**, 2011, 3(2), 531-533.
10. Patel D.M. and Dhaval J.: Formulation and evaluation of fast dissolving film of cetrizine and dextromethorphen, **Int. J. Pharm.**, 2016, 3(9), 3305.
11. Juluru N.S.: Fast dissolving oral films: a review, **Int. J. Adv. Pharm. Biol. Chem.**, 2013, 2(1), 108-112.
12. Rajni B. and Pravin P.:Orally dissolving strips: A new approach to oral drug delivery system, **Int. J. Pharm. Investig.**, 2013, 3(2), 68.
13. Maheshwari R.K.: Potentiation of solvent character by mixed solvency concept: A novel concept of solubilization, **J. Pharm. Res.**, 2010, 3(2), 411-413.
14. Mehtani D. and Maheshwari R.K.: Formulation development and optimization of niosomes using mixed solvency approach for transdermal delivery of poorly soluble drug and its evaluation, **World J. Pharm. Res.**, 2014, 7(3), 234-247.
15. Gupta S. and Maheshwari R.K.: Novel application of mixed solvency concept in the development of fast-release formulation of poorly water-soluble drug using liquisolid technique and its evaluation, **World J. Pharm. Res.**, 2011, 7(3), 225-240.
16. Maheshwari R. K. and Rajagopalan R.: Formulation and evaluation of tinidazole syrup made by mixed solvency concept technique, **Der Pharmacia Lettre.**, 2011, 3(6), 266-271.
17. Jain R., Maheshwari R.K. and George P.: Formulation development and evaluation of controlled release tablets of lamotrigine using mixed solvency concept, **Bull. Pharm. Res.**, 2015, 5(1),14-19.
18. Gahlot N. and Maheshwari R.K.: Formulation and development of vaginal films of poorly water-soluble drug, metronidazole, using mixed solvency concept and their evaluations, **J. Drug Deliv. Ther.**, 2018, 8(6), 41-48.
19. Carpenter G. and Maheshwari R.K.: Formulation and development of fast dissolving oral film of a poorly soluble drug, frusemide with improved drug loading using mixed solvency concept and its evaluation, **J. Drug Deliv. Ther.**, 2018, 8(6),132-141.
20. Kapadia Y.D., Sodha H.P. and Patel V.: Formulation development and evaluation of sublingual film of asenapine maleate, **Int. J. Pharm. Sci**., 2013, 4(3), 1190-209.