

## ENHANCE SOLUBILITY AND PROLONG RELEASE OF PROCHLORPERAZINE MALEATE USING FLOATING NANOEMULSION *IN SITU* GEL

YASSER Q ALMAJIDI<sup>1\*</sup>, AHMED A ALBADERI<sup>1</sup>, HASAN FADHEL<sup>2</sup>

<sup>1</sup>Department of Pharmaceutics, Baghdad College of Medical Sciences, Baghdad, Iraq. <sup>2</sup>Department of Pharmaceutical Chemistry, Baghdad College of Medical Sciences, Baghdad, Iraq. Email: yasser.kasim@yahoo.com

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### ABSTRACT

**Objective:** The objective of this study was to prepare floating gastric *in situ* gel of prochlorperazine maleate (PM) using nanoemulsion technology to improve drug solubility, bioavailability, reduce dosing frequency, and patient compliance.

**Methods:** Eight nanoemulsion formulas (F1–F8) of PM were prepared by ultrasonication method using oil, surfactants: cosurfactants (Smix) with different types, concentrations, and ratios, and deionized distilled water. The nanoemulsion formulas were characterized to select the optimum recipe from which six floating *in situ* gel formulas (floating nanoemulsion *in situ* [FNI] 1-FNI 6) were prepared using sodium alginate as gelling agent, hydroxypropyl methylcellulose (HPMCK) 4M as rate retarding polymer, calcium chloride as cross-linking agent, calcium carbonate as floating agent, and sodium citrate as buffering and neutralizing gastric acid. All FNI formulas were subjected for the evaluation to assess the formulations suitability concerning the dosage form and intended therapeutic purpose.

**Results:** Formulation variables such as the concentration of sodium alginate, HPMCK 4M, calcium carbonate, and calcium chloride affected the gelling properties, formulation viscosity, floating behavior, and *in vitro* drug release. Formulation FNI 6 showed acceptable floating lag time (55±2.3 s) and >12 h floating duration time, and observe prolong release of the drug in *in-situ* gelling preparation.

**Conclusion:** The prepared FNI formulas of PM could float in the gastric conditions and released the drug in a sustained manner. The present formulation was enhanced drug solubility with good retention properties and better patient compliance.

**Keywords:** Prochlorperazine maleate, Nanoemulsion, *In situ* gel, Sodium alginate, Hydroxypropyl methylcellulose 4M.

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### INTRODUCTION

Prochlorperazine maleate (PM) is an antiemetic drug used to suppress nausea and vomiting. It is widely used in motion sickness, drug-induced emesis, post-anesthetic nausea and vomiting, nausea associated with migraines, vomiting and gastroenteritis-induced nausea, malignancy- and cancer chemotherapy-related to vomiting, morning sickness, etc. [1].

It is practically insoluble in water [2] and has short biological half-life 6–8 h. It is mean absolute bioavailability of 12.5% due to extensive liver metabolism [3]. To overcome these problems, many novel drug delivery systems are used to increase water solubility and gastric residence time of the drug.

Oral *in situ* gel-forming system known as stomach specific has provided a suitable way of presenting the controlled drug delivery within the stomach with enhanced gastric retention [4]. One of the most notable among novel drug delivery systems due to many advantages is the *in situ* gelling system such as reduced frequency of drug administration and improved patient compliance [5].

Nanoemulsion is one of the novel approaches to drug delivery to enhance the bioavailability of poorly soluble drugs [6]. It is thermodynamically stable transparent or translucent dispersions of oil and water stabilized by an interfacial film of surfactant and cosurfactant molecules having a globule size of <100 nm [7].

Sonication method is the best way to prepare nanoemulsion. In this method with the help of sonication mechanism, the droplet size of

a conventional emulsion or even microemulsion is reduced. This technique is not suitable for large batches only small batches of nanoemulsion can be prepared by this method [8].

This study aims to formulate the nanoemulsion gastric *in situ* gel of PM to improve drug solubility, bioavailability, and patient compliance, and to reduce its dosage frequency.

### MATERIALS AND METHODS

#### Materials

PM was obtained from Furat pharmaceutical industries, Iraq; hydroxypropyl methylcellulose (HPMC) K4M was purchased from Jiangsu Yew Pharmaceutical Co. Limited, China; calcium carbonate, sodium stearate, sodium alginate, and calcium chloride were obtained from Middle East Laboratories Co. Limited, Iraq. Tween 20, tween 60, tween 80, propylene glycol, poly(ethylene glycols) (PEG) 200, and PEG 400 (J. T Baker, China) were used. Oleic acid, clove oil, lemon oil, lemon oil, turpentine oil, peppermint oil, anise oil, eucalyptus oil, orange oil, cardamom oil, and olive oil (CDH, India) were used. Deionized distilled water (DDW) was used for all the experiments.

#### Methodology

##### Saturated solubility determination

The saturated solubility of PM was performed in different oils including lemon oil, turpentine oil, eucalyptus oil, orange oil, oleic acid, anise oil, clove oil, castor oil, cardamom oil, peppermint oil, and almond oil. Furthermore, the study was also performed on different surfactants including tween 80, tween 60, and tween 20 in addition to varying cosurfactants including PEG 400, PEG 200 and propylene glycol,

Table 1: Composition of PM nanoemulsion

Formula code	Surfactant	Cosurfactant	Smix ratio	Oil type	Oil %v/v	Smix %v/v	DDW %v/v	Drug mg/ml
F1	Tween 80	PEG 400	1:1	Lemon	10	40	50	1
F2	Tween 80	PEG 400	2:1	Lemon	10	40	50	1
F3	Tween 80	PEG 400	1:2	Lemon	10	40	50	1
F4	Tween 60	PEG 400	1:1	Lemon	10	40	50	1
F5	Tween 20	PEG 400	1:1	Lemon	10	40	50	1
F6	Tween 80	PEG 400	1:1	Turpentine	10	40	50	1
F7	Tween 80	PEG 400	2:1	Turpentine	10	40	50	1
F8	Tween 80	PEG 400	1:2	Turpentine	10	40	50	1

F: Nanoemulsion formula code, Smix: Surfactant/cosurfactant mixture. PM: Prochlorperazine maleate

ethanol, butanol, and isopropanol. This was achieved by shaking an excess amount of PM to 5 ml of each of the previous media at 25±10°C for 48 h using magnetic stirrer (500 rpm); finally, the supernatant layer was decanted, filtered, and analyzed using UV spectrophotometer at 254 nm [9].

#### Construction of phase diagrams

Pseudoternary phase diagrams were raised by aqueous titration method to examine the formation of O/W NE using four components: Oil (lemon oil and turpentine acid), surfactant (tween 20, tween 60, and tween 80), cosurfactant (PEG 400), and DDW. The diagrams of triangular coordinate were built using different combination of surfactant/cosurfactant mixtures (Smix) including tween 20: PEG 400, tween 60: PEG 400, and tween 80: PEG 400 at the chosen ratios (1:1, 1:2, and 2:1) as recorded in Table 1. Emulsion area margins were programmed using different ratios of oil to Smix ranging from 9:1 to 1:9 as DDW was added dropwise to the mixture of oleic acid with Smix with gentle stirring. In the case of turbidity appearance, followed by phase separation, the samples were well thought out to be biphasic. If clear and transparent mixtures were visualized after stirring, the examples were considered monophasic. The examples were obvious as points in the phase diagram. The area covered by these points was well thought out to be the nanoemulsion region of existence [10]. The larger the area of the emulsion in the phase diagram was selected as the best nanoemulsion composition for further study due to its better hydration capacity.

#### Preparation of PM nanoemulsion formulas

Different o/w nanoemulsion formulations were prepared by selecting the concentration of oil and Smix according to triangular coordinate diagrams. Primary emulsion was prepared through dissolving 1 mg of PM in lemon oil and turpentine oil separately using magnetic stirrer followed by adding the selected Smix in a fixed proportion reaching at the end to a clear solution. Once again forming a clear emulsion was obtained by adding DDW dropwise into the system at room temperature with continuous stirring (~500 rpm). Then, the prepared solution was subjected to the ultrasonication using a 20 kHz sonicator (Ultrasonics, China) with a supreme power output of 300 W. Sonicator probe was symmetrically immersed into the prepared solution and the sonication process was carried out for 20 min. The continued use of ultrasonication leads to heat generation, this problem resolved by cooling the NE formula container using icebreaker. The best nanoemulsion formula (F6) obtained (Table 1) was subjected to for characterization [10].

#### Preparation of orally floating nanoemulsion *in situ* (FNI) gel

For the development of FNI, the hot method for *in situ* gel preparation was applied. Gelatin polymer (sodium alginate) was added to the prepared selected nanoemulsion formula at 70°C using continuous stirrer until a clear solution was obtained. Then, the cross-linking agents (calcium chloride and sodium stearate), gas-generating agent (calcium carbonate), and floating agent (HPMC K4M) were added to the polymeric solution after cooling <40°C under constant stirrer to make the same cluster. The gel formation occurred by the solution cooling to 25°C [11]. Six FNI formulas were prepared (Table 2).

Table 2: Composition of PM FNI gel

Ingredient (%w/v)	FNI 1	FNI 2	FNI 3	FNI 4	FNI 5	FNI 6
Prochlorperazine maleate	0.1	0.1	0.1	0.1	0.1	0.1
Sodium alginate	2	3	3	2	3	3
Calcium chloride	0.5	0.5	0.5	1	1	1
Calcium carbonate	1.5	1.5	2	1.5	1.5	2
HPMC K4M	1	1	1	2	2	2
Sodium stearate	1	1	1	1	1	1

PM: Prochlorperazine maleate, FNI: Floating nanoemulsion *in situ*, HPMC: Hydroxypropyl methylcellulose

#### Characterization of the optimum PM nanoemulsion

Measurement of the conductivity of the selected nanoemulsion formula was performed using manual conductivity meter. Turbidity analysis of the selected nanoemulsion formula was carried out by measuring the absorbance of undiluted samples at 650 nm (light wavelength) using a UV-visible spectrophotometer (UV-visible spectrophotometer Shimadzu 1650 pc - Japan). For zeta potential analysis, all the samples were diluted with DDW before use. Zeta potential, droplet size, and polydispersity index measurements were done using Zetasizer Nano ZS (Malvern, UK). The whole experiments were carried out at 25°C in triplicate.

#### Characterization of the orally FNI gel

##### Content uniformity test

Accurately, 1 ml of each FNI formulas (equivalent to 1 mg PM) was taken in 10 ml volumetric flask separately, then dilute up to 10 ml with (pH 1.2) HCl solution, then made further dilution with HCl solution if required. Contents of PM were determined spectrophotometrically using double-beam UV-visible spectrophotometer (Shimadzu 1650 PC - Japan) at  $\lambda_{max}$ =254 nm [12]. All measurements were made in triplicate, and the average reading  $\pm$ SD was recorded.

##### Determination of pH

The pH of all FNI gel formulas was determined using a calibrated pH meter. The readings were taken for an average of three samples.

##### Viscosity measurement of FNI gel

Viscosities of the FIN formulas were determined using a Brookfield viscometer. Analyses were performed using spindle number 4, and the temperature was maintained at 25±1°C. All analyses were made in triplicate and the average reading  $\pm$ SD was recorded after 30 s [13].

##### *In vitro* gelation study

Accurately, 10 mL of each of the prepared FNI gel formulas was added to 100 mL of 0.1 N HCl (pH 1.2) at 37°C in a beaker with a mild stirrer (50 rpm) to avoid breaking of formed FNI. Gelling capacity was calibrated in three groups depending on the gel stiffness, gelation time, and duration as such

- (+) gelation happens after few minutes, stays for few minutes and rapidly dispersed.
- (++) gelation happens immediately and continues for few hours.
- (+++) gelation happens immediately and continues for an extended period [14].

### In vitro floating study

USP dissolution apparatus (Karl Kolb, Germany) having 900 ml of simulated gastric fluid (0.1 N HCl, pH 1.2) was used to determine the *in vitro* floating study. The Petri dish containing 5 ml of withdrawn *in situ* gelling solution was immersed into dissolution apparatus at 37°C. A visual determination was considered for the time taken by the formulation to emerge on the medium surface and the time taken to the formulation constantly to float on the dissolution medium surface. The whole measurements were made in triplicate and the average reading $\pm$ SD was recorded [15].

### In vitro drug release study

The dissolution test apparatus USP Type II (Paddle Method, Karl Kolb, Germany) was carried to performed the *in vitro* release study. The volume of dissolution media was 900 ml (0.1 N HCl, pH 1.2) at 37 $\pm$ 0.2°C, with a speed of 50 rpm.

About 1 ml of the sample was removed at a time interval (15 min, 30 min, 45 min, 1 h, 2 h, 4 h, 8 h, and 12 h) and immediately replaced with fresh dissolution medium. The spectrophotometric methodology was used to

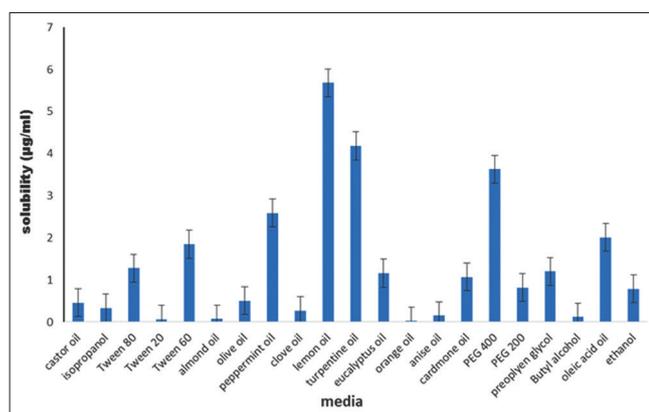


Fig. 1: Saturated solubility of prochlorperazine maleate in different media (results are expressed as mean  $\pm$  SD, n=3)

determine the drug content in the withdrawn sample using a UV-visible spectrophotometer at  $\lambda$  max 254 nm. All measurements were made in three readings and the average reading  $\pm$ SD was recorded [16].

## RESULTS AND DISCUSSION

### Saturated solubility determination

Fig. 1 clearly demonstrates the solubility of PM in different oil, surfactants, and cosurfactants. The significantly higher solubility of the drug in lemon oil then turpentine oil compared to other oils. On the other hand, the drug possesses higher solubility in tween 80 due to the higher HLB value of 16.7 and hence greater hydrophilicity compared to the different grades having lower HLB values (15, 14.9, and 16.7) for tween 80, tween 60, and tween 20, respectively [17]. Furthermore, the significantly higher solubility of the drug in the cosurfactant is arranged in the order of PEG 400 > PEG 200 > ethanol > isopropanol > butanol which might be due the higher molecular weight and hydrophilicity of PEG 400 compared to the others [18].

### Construction of phase diagrams

The used oily phase is lemon oil and turpentine oil based on solubility study, and only one part of the oil was used since the increase in oil phase causes an increase in  $S_{mix}$  %v/v. Fig. 2 showed the triangular coordinate diagram for the o/w emulsions prepared using lemon oil and turpentine oil separately as the oil phase and different surfactant: cosurfactant ( $S_{mix}$ ) ratios. The best result is obtained using turpentine oil, tween 80:PEG 400 ( $S_{mix}$  1:1), and DDW which shows the largest stable emulsion area. Tween 80 (HLB 15) is a non-ionic surfactant which has both a hydrophilic and a lipophilic part in their chemical structure, and it is concentrated and adsorbed onto the oil (turpentine oil: water) interface to provide a protective barrier around the dispersed droplets in o/w emulsion. Hence, it stabilizes the emulsion by reducing the interfacial tension ( $\gamma$ ) of the system, and it is imparting a charge on the droplet surface which reducing the physical contact between the droplets and decreasing the potential for coalescence [19].

### Characterization of the optimum PM nanoemulsion

The nanoemulsion formula F6 (oil: surfactant-cosurfactant: water, 10:40:50) was selected as the optimized formula as it displayed

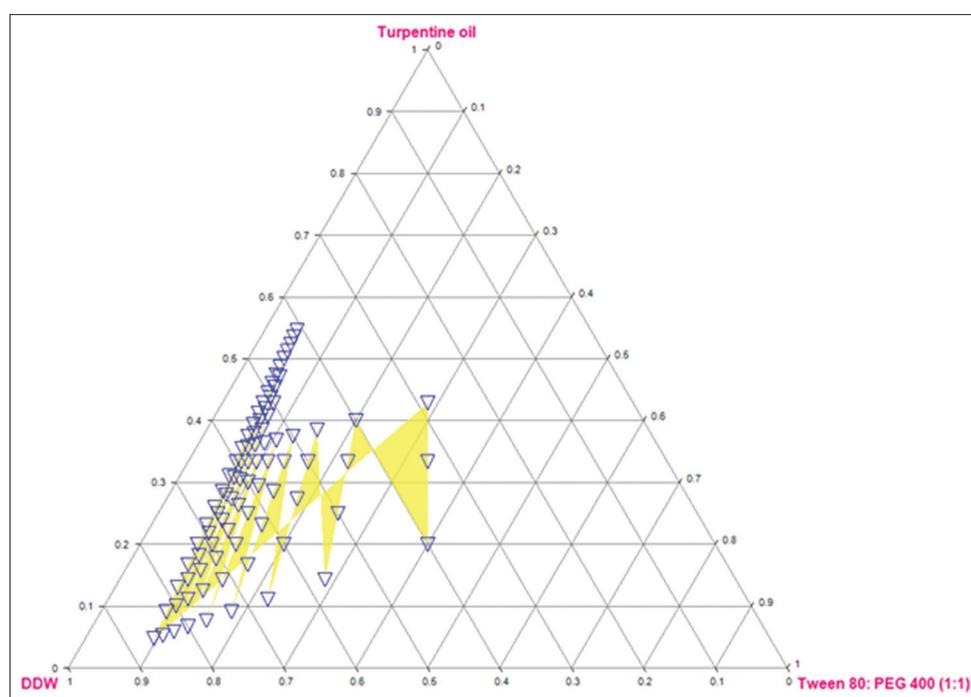


Fig. 2: Triangular coordinate diagrams of the largest o/w emulsion area prepared using turpentine oil, tween 80:PEG 400 ( $S_{mix}$  1:1), and DDW

optimum response variables of 99.82% optical transparency,  $210 \pm 3.7 \mu\text{s}/\text{cm}$  electrical conductivity, low droplet size ( $25.5 \pm 2.12 \text{ nm}$ ), polydispersity of  $0.127 \pm 0.02$ , and zeta potential about  $-8.0 \pm 0.81$ .

**Characterization of the orally FNI gel**

*Content uniformity test*

Drug content of all FNI formulas is given in Table 3. These results agreed with the requirements of USP indicating high content uniformity of the prepared recipes and adequacy of the preparation method [20].

*Determination of pH*

It is essential to measure the pH for oral preparation to avoid the throat irritation. All FNI gel formulas have a pH neutral or slightly basic. The results of pH for all FNI formulas are shown in Table 3.



**Fig. 3:** Photographs were taken during the *in vitro* floating study of floating nanoemulsion *in situ* gel formulas in 100 ml 0.1 N HCl (pH 1.2)

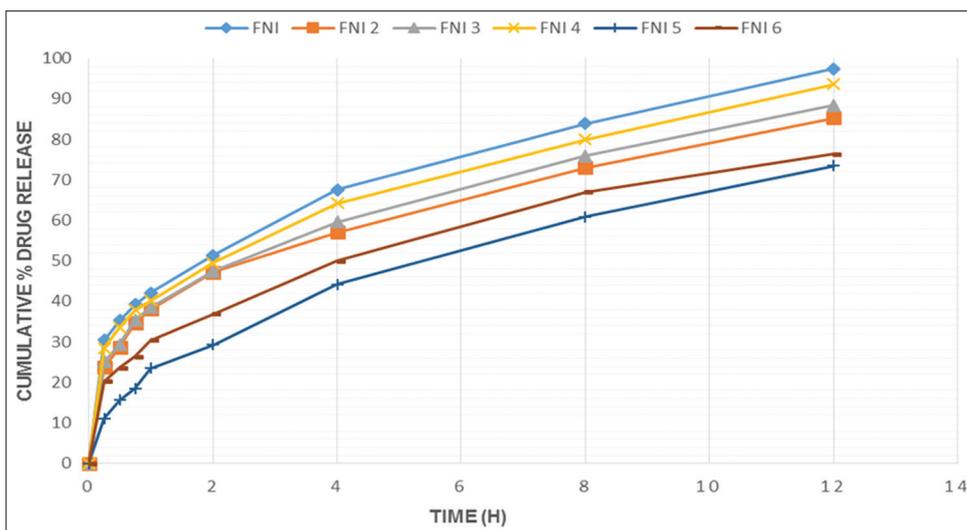
*Viscosity measurement of FNI gel*

The viscosity is an essential variable because it affects the gelation of the solution, the flow of the formulation, and time required for gelation[21]. The ease of swallowing FNI liquid primarily depends on the rheological properties of the solutions, and such similar fluid undergoes a rapid sol-gel transition due to ionic interaction with direct contact with stomach contents. Table 3 shows the results of the viscosities of all FNI formulas. Different concentrations of  $\text{CaCl}_2$  and  $\text{CaCO}_3$  showing non-significant ( $p > 0.05$ ) increase in viscosity because Na alginate forms strong crosslinking in the polymer matrix. As the concentration of Na alginate (1%, 2%, and 3%) increases were found to be also increased. HPMC K4M was selected for preparation to maintain viscosity.  $\text{CaCl}_2$  on the contact with 0.1 N HCl (pH 1.2), the liquid polymeric solutions undergo a fast sol-to-gel transition by ionic gelation without affecting viscosity [22].

*In vitro gelation study*

0.1 N HCl (pH 1.2) medium was used to carry out the gelling studies and the data obtained were then represented in Table 3. All FNI gel formulas showed immediate gelation on contact with the acidic medium, and the formed gel preserved their integrity. Gelation occurs when the insoluble calcium chloride solubilizes when it comes in contact with acidic medium releasing calcium ions. The anionic polymer (sodium alginate) in the formulation interacts with the calcium ions causing instantaneous gelation and provides a gel barrier that restricts drug release [23].

On increasing concentration of  $\text{CaCl}_2$  (FNI 4-FNI 6) significantly increased gel strength and decreases gelation time ( $p > 0.05$ ) due to increase in gel rigidity as the degree of cross-linking of divalent  $\text{Ca}^{2+}$  ions with the polymer chains increases and thus causing gelation to undergo instantly[24].



**Fig. 4:** *In vitro* drug release profile for floating nanoemulsion *in situ* gel formulas in 0.1 N HCl (results are expressed as mean  $\pm$  SD, n=3), ( $p > 0.05$ ).

**Table 3:** *In vitro* evaluation of FNI gel formulas of PM

FNI Formulation	Content uniformity %	pH	Viscosity	Graded gel response	Floating lag time (s)	Floating duration time (h)
FNI 1	$97.56 \pm 0.29$	$7.2 \pm 0.3$	$29823 \pm 4.7$	++	$73 \pm 4.3$	>12
FNI 2	$97.75 \pm 0.43$	$7.2 \pm 0.2$	$32458 \pm 2.3$	++	$88 \pm 2.1$	>12
FNI 3	$99.20 \pm 0.23$	$7.3 \pm 4$	$33546 \pm 5.3$	++	$40 \pm 1.15$	>12
FNI 4	$98.74 \pm 0.45$	$7.2 \pm 0.8$	$34654 \pm 2.8$	+++	$103 \pm 3.5$	>12
FNI 5	$97.91 \pm 0.30$	$7.3 \pm 3.2$	$35965 \pm 2.3$	+++	$109 \pm 1.15$	>12
FNI 6	$98.58 \pm 0.47$	$7.3 \pm 0.5$	$39785 \pm 3.4$	+++	$55 \pm 2.3$	>12

n=6 (mean $\pm$ SD). PM: Prochlorperazine maleate, FNI: Floating nanoemulsion *in situ*

### In vitro floating study

The formulated FNI gel employed  $\text{CaCO}_3$  as a gas-generating agent. The *in vitro* floating test exposed the ability of all FNI formulas to maintain buoyant for >12 h (Table 3 and Fig. 3). Instantaneously, gas generation was formed due to the reaction between sodium stearate and calcium carbonate. These gases were trapped in the rigid structure of gel which has buoyant behavior in dissolution media for prolong time sufficiently for up to 12 h or >12 h.

The observed behavior suggests that the gel formed by the combination of sodium alginate with the investigated polymer enabled efficient entrapment of  $\text{CO}_2$  gas producing a buoyant preparation with shorter free lag time which can remain in the stomach for a more extended period and assist the controlled release of the drug [25].

### In vitro drug release study

The *in vitro* release study of PM from all FNI gel formulas in 0.1 N HCl (pH 1.2) was conducted for a period of 12 h, and the results are shown in Fig. 4. The release of drug from these formulae was characterized by an initial phase of high release (burst effect) followed by the second phase of moderate release. This biphasic pattern of release is a characteristic feature of matrix diffusion kinetics [26].

The effect of polymer concentration on *in vitro* drug release from *in situ* gel formulations is shown in Fig. 4. A significant decrease in the rate of drug release was observed with the increase in polymer concentration, and it was attributed to the rise in the density of the polymer matrix. The increase in HPMC concentration promotes the formation of highly viscous gels on contact with aqueous fluids which will produce more retardation in drug release rate [27].

The FNI 6 was selected as the optimum formula since it shown more sustained drug release (71.53% after 6 h) with burst effect, acceptable lag time (55 s), and good gel strength that withstand peristalsis for a long time.

### CONCLUSION

In the present study, various in FNI gelling liquid oral formulations of PM was prepared. The research has shown that by applying nanoemulsion technology, the solubility of low soluble drug PM increases (Class II) due to smallest droplet size formed by high-energy method (ultrasonication), hence, dissolution and absorption of the drug. The selected prepared FNI gel of PM (FNI 6) gives burst effect and sustained release. It appears to be promising as a stomach-specific delivery system of PM for better prevention of nausea and vomiting with a small dose, less dose frequency, and more patient compliance.

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### AUTHORS' CONTRIBUTION

All the authors contributed equally in the conceptualization and execution of the review article.

### CONFLICTS OF INTEREST

The authors declared that they have no conflicts of interest.

### REFERENCES

- Jain CP, Joshi G, Kataria U, Patel K. Enhanced permeation of an antiemetic drug from buccoadhesive tablets by using bile salts as permeation enhancers: Formulation characterization, *in vitro*, and *ex vivo* studies. *Sci Pharm* 2016;84:379-92.

- Moffat AC, Osselton MD, Widdop B. Clarke's Analysis of Drugs and Poisons in Pharmaceuticals, Body Fluids, and Postmortem Material. 4<sup>th</sup> ed. Pharmaceutical Press; 2011.
- Albadry AA, Ali WK, Al-saady FA. Formulation and Evaluation of Prochlorperazine Maleate Sustained Release Floating Tablet. *Int J Pharm Pharm Sci* 2017;9:89-98.
- Rathod SH, Dhruvi P, Mehta, Yadav JS. A Review on stomach specific floating *in-situ* gel. *Indian J Pharm Sci* 2014;6:19-30.
- Sarada K, Firoz S, Padmini K. *In-situ* gelling system: A review. *Int J Curr Pharm Res* 2015;5:76-90.
- Mahajan HS, Savale SK. Nanoemulsions: A versatile mode of drug delivery system. *Indian J Nov Drug Deliv* 2016;8:123-32.
- Savardekar P, Bajaj A. Nanoemulsions-a review. *Int J Res Pharm Chem* 2016;6:312-22.
- Sharma N, Bansal M, Visit S, Sharma PK, Kulkarni GT. Nanoemulsion: A new concept of the delivery system. *Chron Young Sci* 2010;1:2-6.
- Almajidi YQ, Mahdi ZH, Marie NK. Preparation and *in vitro* evaluation of montelukast sodium oral nanoemulsion. *Int J App Pharm* 2018;10:49-53.
- Beg S, Harikrishna D, Svitlana S, Feng Z, Jessica M, Galina G, et al. Ultrasonic emulsification of food-grade nanoemulsion formulation and evaluation of its bactericidal activity. *Colloids and Surfaces B Biointerfaces* 2013;101:414-23.
- Sarwar BC, Sidharth SJ, Ch NP, Mohammad R, Suryakanta S, Sruti J, et al. Development of solid self-nano emulsifying granules (SSNEGs) of ondansetron hydrochloride with enhanced bioavailability potential. *Colloids Surf B* 2013;101:414-23.
- Chand P, Gnanarajan PG, Kothiyal P. *In situ* gel: A review. *Indian J Pharm Biol Res* 2016;4:11-9.
- Chaniyara S, Modi D, Patel R, Patel J, Desa R, Chaudhary S. Formulation and evaluation of floatable *in situ* gel for stomach-specific drug delivery of ofloxacin. *Am J Adv Drug Deliv* 2013;1:285-99.
- Maheswaran A, Padmavathy J, Nandhini V, Saranana D, Angel P. Formulation and evaluation of floating oral *in situ* gel of diltiazem hydrochloride. *Int J App Pharm* 2017;9:50-3.
- Jamee N, Kiran R, Kuchana V. Formulation and evaluation of floating oral *in-situ* gel of ranitidine hydrochloride. *Indian J Palliative Care* 2016;6:75-81.
- Kajale AD, Chandewar AV. Design development and evaluation of gastro-retentive oral floating *in-situ* gel of metoprolol succinate. *Indo Am J Pharm Sci* 2016;6:5536-48.
- Allen LV, Popovich NG, Ansel HC, editors. Disperse System. Philadelphia, PA: Lippincott Williams and Wilkins Publishing; 2011.
- Ma TY, Hollander D, Krugliak P, Katz PK. PEG 400, a hydrophilic molecular probe for measuring intestinal permeability. *Gastroenterology* 1990;98:39-46.
- Maraie NK, Almajidi YQ. Application of nanoemulsion technology for preparation and evaluation of intranasal mucoadhesivenano-*in situ* gel for ondansetron HCl. *J Global Pharma Technol* 2018;10:431-42.
- United States Pharmacopeia. (USP 30) and the 25<sup>th</sup> edition of the National Formulary (NF25). USA: United States Pharmacopeial Convention Publishing; 2007.
- Bobade NN, Pande SD. Formulation and evaluation of controlled release gastro-retentive *in situ* gel for diltiazem hydrochloride. *Indian J Pharm Educ Res* 2016;50:254-65.
- Reddy RA, Ramesh B, Kishan V. Drug-excipient interaction during formulation development, *in vitro* and *in vivo* evaluation of gastroretentive drug delivery system for nizatidine. *Int J Pharm Sci Nanotech* 2013;6:2281-93.
- Choi BY, Park HJ, Hwang SJ, Park JB. Preparation of alginate beads for the floating drug delivery system: Effects of  $\text{CO}_2$  gas-forming agents. *Int J Pharm* 2002;239:81-91.
- Wamorkar V, Varma MM, Manjunath SY. Formulation and evaluation of stomach specific *in situ* gel of metoclopramide using natural, biodegradable polymers. *IJRPBS* 2011;2:193-201.
- Rajinikanth PS, Mishra B. Floating *in situ* gelling system for stomach site-specific delivery of clarithromycin to eradicate H. Pylori. *J Control Release* 2008;125:33-41.
- Shastri DH, Dodiya HD, Shelat P, Priya AK. Formulation development and evaluation of a gastroretentive *in situ* oral gel of cefuroxime axetil. *J Young Pharm* 2016;8:324-29.
- Thomas LM. Formulation and evaluation of floating *in-situ* gel of metronidazole. *Int J Pharm Pharm Sci* 2014;6:265-9.