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Research Article

FORMULATION AND EVALUATION OF FLOATING *IN SITU* GEL OF OMEPRAZOLE MAGNESIUM FOR ORAL DRUG DELIVERY SYSTEM

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ABSTRACT

Objective: Omeprazole magnesium is indicated for the treatment of erosive esophagitis associated with gastroesophageal reflux disease. It is one of the highly prescribed proton pump inhibitor in the management of peptic ulcer diseases. The therapeutic concentration of a drug in blood can be maintained for a prolonged period of time by administering it in the form of *in situ* floating gel dosage form. Omeprazole magnesium undergoes degradation at a low pH of the esophagus and stomach; it is therefore given as *in situ* gel, so, there is minimum contact with acidic pH.

Methods: Omeprazole magnesium suspension prepared using various polymers and floating agents in varying concentrations. Several evaluation tests including dissolution test to ensure the release of the drug from formulation by *in vitro* technique, color and homogeneity, *in vitro* floating duration, *in vitro* gelling capacity, drug content determination, pH of the formulation, and floating lag time were studied.

Results: All formulations demonstrated good Fourier-transform infrared compliance and no interaction between drug, polymer, and other excipients. The study's findings show that the formulation F6 showed the best results.

Conclusion: The developed formulation was a viable alternative conventional solution by virtue of its ability to enhance bioavailability through its longer gastric residence time and ability to sustain drug release as well as the advantage of floating and pH which minimize the degradation of omeprazole magnesium which is easily degraded by acidic environment.

Keywords: *In situ* gel, Gastroesophageal reflux disease, omeprazole magnesium, Polymers, *In vitro* floating duration, *In vitro* gelling capacity bioavailability, Gastric resident time.

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INTRODUCTION

Floating systems are low-density systems with sufficient buoyancy to float over the gastric contents without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system [1].

Floating system results in an increased gastric retention time and a better control of the fluctuations in plasma drug concentration. Minimal gastric content is required to allow proper achievement of the buoyancy retention principle and a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal. Formulation of gastro retentive *in situ* gel system involves the use of gelling agent which can form a stable sol/suspension system to contain the dispersed drug and other excipients. The gelling of this sol/suspension system is achieved in gastric environment, triggered by ionic complexation due to change in pH [2].

Gastroesophageal reflux is the involuntary movement of gastric contents to the esophagus (Fig. 1). Gastroesophageal reflux is a normal physiological process that occurs several times a day without symptoms or damage of the esophageal mucosa in most otherwise healthy individuals. Gastroesophageal reflux disease is a condition in which reflux of gastric contents into the esophagus produces frequent or severe symptoms that negatively affect the individual's quality of life or result in damage to esophagus, pharynx, or the respiratory tract [3].

Omeprazole magnesium (Fig. 2) is a benzimidazole with selective and reversible proton pump inhibition activity. It forms a stable disulfide bond with the sulfhydryl group of the hydrogen-potassium (H+ - K+) ATPase found on the secretory surface of parietal cells, thereby inhibiting the final transport of hydrogen ions (through exchange with potassium ions) into the gastric lumen and suppressing gastric acid secretion [4].

METHODS

Omeprazole magnesium was kindly provided by Dr Reddy's Laboratories, Hyderabad, sodium carbonate sodium alginate, methyl paraben, and propyl paraben were procured from Arora and company, Delhi, Sodium citrate and Hydrochloric Acid form Central Drug House (P) Ltd., New Delhi, Calcium chloride from Loba Chemicals, Mumbai. All chemical and reagents used were of analytical grade. De-ionized water was used for the complete study.

Preformulation studies

Preformulation studies required to ensure the development of a stable as well as therapeutically effective and safe dosage form. These studies focus on the physicochemical properties of the drug that could affect performance and development of an efficacious dosage form.

Description of drug

Organoleptic properties of drug, that is, color, odor, and taste were observed.

Identification of drug

- UV spectrophotometric analysis of drug
  Ultraviolet absorption in the range 200–400 nm of a 100 µg/ml solution of the drug in 0.1 N HCl was determined [5].
- Fourier-transform infrared (FTIR) analysis of drugs

The FTIR analysis of the sample was carried out for qualitative compound identification in ATR based Brukers Tensor 27 instrument. The samples were kept at room temperature (initially) and at 50°C for 15 days before study.

Analytical estimation of drug

- Determination of absorption maxima (λ max)/wavelength maxima
  The standard stock solution of omeprazole magnesium was prepared by dissolving 10 mg of drug in 0.1N HCl in 100 ml volumetric flask. Stock solution of omeprazole magnesium was further diluted in 0.1 N HCl to get standard solution of 100 µg/ml. The resulting solution was then scanned between 200 and 400 nm UV visible spectrophotometer (shimadzu 1700).

- Preparation of standard calibration curve of Omeprazole magnesium Omeprazole magnesium (10 mg) was dissolved in (0.1 N HCl, pH 1.2) and volume was made up to 100 ml in 100 ml volumetric flask. This solution (100 µg/ml) was further diluted with (0.1 N HCl, pH 1.2) to obtain solution of 10–50 µg/ml. The absorbance of each solution was measured at λ_{max} 348.5 nm using UV spectrophotometer. The standard curve was obtained by plotting absorbance versus concentration (µg/ml).

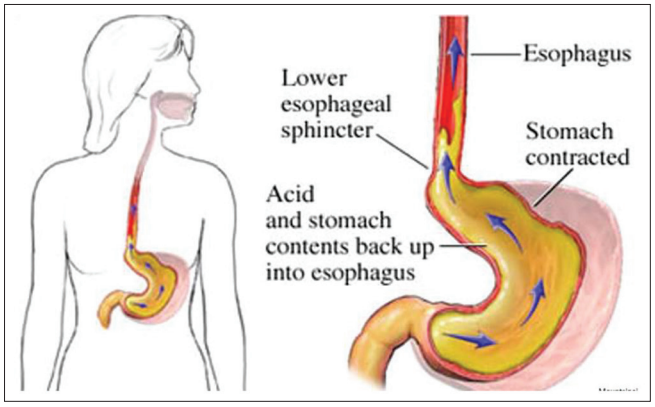

Fig. 1: Gastroesophageal reflux disease

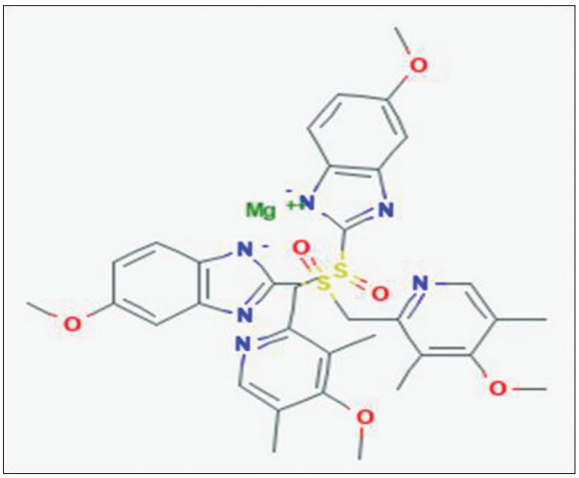

Fig. 2: Structure of omeprazole magnesium

- Melting point determination
  Melting point of omeprazole magnesium was determined using melting point apparatus. The pre-sealed capillary filled by the small amount of drug, the capillary, and thermometer placed in melting point apparatus. The temperature noted when the drug starts to melt and till complete melt. The standard melting point is between 199 and 201°C (USP, 2005).

- Solubility determination
  For quantitative solubility studies, known amount of drug (10 mg) was suspended in solvents, that is, water, 0.1 N HCl. The solutions were stirred for 48 h on magnetic stirrer under thermostat. To separate phases, the solutions were left to sediment for 24 h under thermostat circumstances. The absorption of diluted aliquots was measured with UV spectrophotometer [6,7].

- Drug-polymer compatibility study
  The possible interaction between the drug and excipients was studied by infra-red spectroscopy. The equal quantity of drug and excipient was kept at 50°C for 15 days and the same quantity of both to prepare fresh immediate samples was taken and spectra were observed for compatibility [8].

Formulation and evaluation of *in situ* gel

Fabrication of omeprazole magnesium in situ gel

Omeprazole magnesium suspension prepared using various polymers and floating agents. Sodium alginate solution of different concentrations (0.50–1.5 g) prepared in deionized water containing sodium citrate (0.25 g) and calcium chloride (0.016 g). The sodium alginate dispersed in deionized water, heated up to 90°C with stirring continuously on magnetic stirrer and then cooled below 40°C various concentrations of calcium carbonate and drug was added after cooling the solution below 40°C with continuous stirring to form uniform dispersion. Total nine formulations (Table 1) were prepared and evaluated [9].

Evaluation and characterization of floating *in situ* gel

Physical appearance

Sodium alginate based *in situ* suspension was visually checked for their clarity, that is, color, homogeneity.

pH of in situ solution

The pH was measured for sodium alginate based *in situ* suspension using a pH meter. The pH of each suspension was determined in triplicates.

In vitro gelling capacity

To evaluate the formulations for their *in vitro* gelling capacity by visual method, suspension of *in situ* gel forming drug delivery system was prepared. The *in vitro* gelling capacity of formulations was measured by

Table 1: Formulae of formulation

Formulation code Ingredient ↓	F1	F2	F3	F4	F5	F6	F7	F8	F9
Omeprazole magnesium (g)	0.100	0.100	0.100	0.100	0.100	0.100	0.100	0.100	0.100
Sodium alginate (g)	0.50	1.0	1.5	0.50	1.0	1.5	0.50	1.0	1.5
Tri-sodium citrate (g)	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Calcium chloride (g)	0.016	0.016	0.016	0.016	0.016	0.016	0.016	0.016	0.016
Calcium carbonate (g)	0.25	0.25	0.25	0.75	0.75	0.75	1.5	1.5	1.5
Methyl paraben (g)	0.18	0.18	0.18	0.18	0.18	0.18	0.18	0.18	0.18
Propyl paraben (g)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Water q.s. (ml)	50	50	50	50	50	50	50	50	50

placing 5 ml of the gelation solution (0.1 N HCl) in a 15 ml borosilicate glass test tube and maintained at 37±1°C temperature. 1 ml of formulation suspension was transferred slowly by placing the pipette at surface of fluid in test tube. As the suspension comes in contact with gelation solution, it immediately converted into stiff gel like structure. The gelling capacity of solution was evaluated on the basis of stiffness of formed geland time period for which formed gel remains as such. The *in vitro* gelling capacity was graded in three categories on the basis of gelation time and time period for which formed gel remains [10].

(+) Gels after few minutes, dispersed rapidly, (++) Gelation immediate remains for 12 h, (+++) Gelation immediate remains for more than 12 h.

In vitro floating duration

The *in vitro* floating study was determined using USP dissolution apparatus II having 900 ml of Hydrochloric acid (0.1 N). The temperature of the dissolution medium was kept at 37°C and 10 ml prepared *in situ* gel formulations were transferred. Time for the formulation took to emerge on the medium surface (floating lag time) and the time the formulation constantly floated on the dissolution medium surface (duration of floating) was noted.

Floating lag time

The floating lag time is defined as time taken by the gel to reach the top from bottom of the dissolution flask. The floating lag time is determined by visual inspection in a USP (Type II) dissolution test apparatus containing 900 ml of 0.1 N HCl at 37°C.

Determination of drug content

The 5 ml of the suspension was added to 100 ml (0.1N HCl, pH 1.2) solution and stirred for an hour on magnetic stirrer. The suspension was filtered and the drug concentration was determined using UV-visible spectrophotometer at λ_{max} 348.5 nm against a suitable blank solution [11].

In vitro drug release study

The release of omeprazole magnesium from sustained release suspension was determined using dissolution apparatus I (basket covered with muslin cloth) at 50 rpm. The rotation speed was slow enough to avoid breaking of gelled formulation and maintained at mild agitation conditions as remains at *in vivo*. The 900 ml dissolution medium of 0.1N HCl was maintained at 37°C±0.5°C temperature. A sample (5 ml) of solution was withdrawn from the dissolution apparatus at 0 min, 15 min, 30 min, 45 min, 60 min, 1 h, 2 h, 3 h, 4 h, 5 h, 6 h, 8 h, 10 h, and 12 h of dissolution. The samples were filtered through Whatman filter paper and analyzed using UV method. Cumulative percentage of drug release was calculated [2].

Selection of best formulations

On the basis of various evaluation parameters, namely floating lag time and *in vitro* release study two formulations were found to be optimum for the further study, that is, F3 and F6. These formulations were formulated and evaluated for physical appearance, pH of *in situ* solution, drug content, *in vitro* floating duration, floating lag time, and *in vitro* drug release study of the formulations. On the basis of dissolution, F3 was found to be having less drug release as well as drug content as compared to F6, thus F6 was selected as the final formulation.

Study of marketed formulation and its comparison with final formulation

OMEZ Insta 20 mg by Dr. Reddy's was the available marketed preparation. This product was taken as the standard and was compared with the final formulation with respect to evaluating parameters, namely, *in vitro* drug release, drug content, release kinetics, similarity factor, and difference factor.

Drug content uniformity

The entire sachet was dissolved in 100 ml 0.1 N HCl and kept for 2 h. The solution was filtered and filtrate (5 ml) was diluted to 10 ml. Absorbance of the resulting solution was measured with a UV-Visible spectrophotometer UV-1700 (Shimadzu, Japan) at λ_{max} 348.5 nm.

In vitro drug release

A USP dissolution apparatus type II was employed to study *in vitro* drug release. The dissolution medium used was 900 mL of 0.1N HCl, 37 ± 0.5°C temperature at stirring rate 50 rpm.

Kinetic modeling

Model independent methods

A simple model independent approach uses a difference factor (f1) and a similarity factor (f2) to compare dissolution profiles.

a) Difference factor

The difference factor calculates the percentage difference between the two curves at each time point and is a measurement of the relative error between the two curves. Reference values are given in Table 2. It is calculated by formulae:

$f1 = \Sigma(\text{Rt-Tt})/\Sigma Rt \times 100$

b) Similarity factor

The similarity factor is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percentage dissolution between the two curves, that is, test - reference. It represents closeness of two comparative formulations. Reference values are given in Table 2. It is calculated by formulae:

$$f_2 = 50 \times \log\left\{\left[1 + \frac{1}{n}\sum_{t=1}^{n}(R_1 - T_1)^2\right]^{-5} \times 100\right\}$$

Model dependent methods

Model dependent methods are based on different mathematical function, which describes the dissolution profile. The dissolution profiles are evaluated depending on the derived model parameters. The model dependent approach included zero order, first order, Higuchi, and Korsmeyer–Peppas model.

Release kinetics described the overall release of the drug from the dosage forms. As qualitative and quantitative changes in a formulation may alter drug release and *in vivo* performance, developing tools that facilitate products development by reducing the necessity of bio-studies is always desirable. In this regard, the use of *in vitro* drug dissolution data to predict *in vivo* bio-performance can be considered as the rational development of controlled release formulations.

Data obtained from the *in vitro* release studies were fitted to various model dependent kinetics equations such as zero order, first order, Higuchi model, and Korsmeyer–Peppas model which are shown below.

Zero order model $Q_t = Q_o + K_o t$

First order model $\log C = \log C_o - Kt/2.303$

Higuchi model $Q = K_H \times t^{½}$

Korsmeyer–peppas model $Q/Q_o = Kt^n$

Where, K_o to K_H were release rate constants, Q/Qo was fraction of drug released at time t, K was a constant and n was diffusion constant that indicates general operating release mechanism. For Fickian (diffusion controlled), n ≤ 0.5; for non Fickian release, "n" value is in between 0.5

Table 2: Comparison of dissolution profiles

f1	f2	Inference
0	100	Dissolution profiles are identical
≤15	≥50	Similarity or equivalence of two profiles

to 1.0; for zero order release, n=1; for super case transport II, n>1.040. Based on the slope and the r^2 values obtained from the above models the mechanism of drug release was decided [12,13].

RESULTS AND DISCUSSION

Preformulation studies

Description of drug: The observed parameters are reported in Table 3.

Identification of drug

a) UV spectrophotometric analysis of drug
Photometric spectrum shows by data analysis that the there is only one significant peak which is clearly distinguishable and obtained at 348.5 nm. Hence, absorption maxima (λ_{max}) of omeprazole magnesium are meant to be 348.5 nm.

b) FTIR spectrum method
Drug and polymers identified by IR spectrum method which are compared with its standard IR given in pharmacopeia. These IR spectra given below (Table 4) shown that the peaks obtained in these spectra (Fig. 4) are similar to that given in standard (Fig. 3).

Analytical methods of estimation

Analytical methods obey Beer's law and found suitable for the study. Standard calibration curve of omeprazole magnesium was prepared in 0.1 N HCl.

Determination of absorption maxima (λ_{max})/wavelength maxima

The λ_{max} of given sample of omeprazole magnesium (348.5 nm) and standard value (345.42 nm) found to be similar hence drug is omeprazole magnesium.

Preparation of standard calibration curve of omeprazole magnesium

The standard curve was obtained by plotting absorbance versus concentration (µg/ml; Table 5).

Solubility determination

Omeprazole magnesium was very slightly soluble in water (1 mg in 100 ml), readily soluble in 0.01 N HCl (10 mg in 100 ml).

Melting point determination

Melting point of omeprazole magnesium was found to be in the range of 199–201°C.

Table 3: Description of drug

S. No.	Properties	Inference
1.	Color	White
2.	Odor	Odorless
3.	Taste	Bitter

Table 4: Interpretation of infrared spectrum of omeprazole magnesium

S. No	Peaks (cm-1)		
	Absorbance assignment	Reported	Observed
1	C=C aromatic stretching	1591	1591
2	methyl C-H stretching	2944	2931
3	out of plane bending of aromatic ring bonds	850	843.97
4	symmetrical C-H bending	1410	1412.35
5	symmetrical C-H bending	1477	1483.15
6	-C-O-C- asymmetrical stretching	1034	1065.56
7	strong –S=O stretching,	1014	1011.22
8	C=N hetero aromatic stretching of pyridine	1613	1613

Drug-excipient compatibility study

FTIR spectrum shows the peaks of pure drug sample and polymers as compared to standard drug samples, that is, no chemical reaction occurs between polymers and drug samples (Table 6).

Evaluation of prepared *in situ* gels

The color, homogeneity, pH, gelling capacity, floating time, floating lag time, and drug content observed are as following in Table 7.

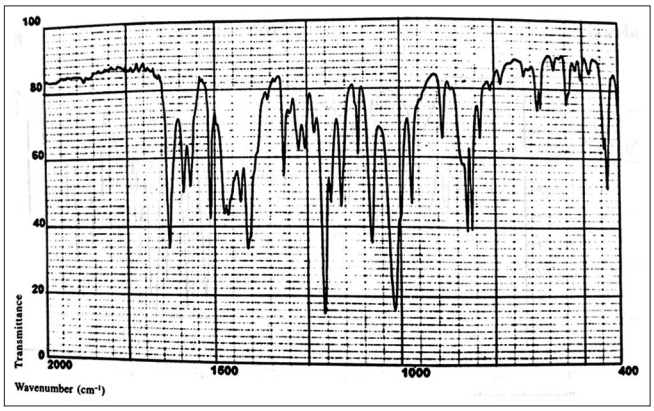

Fig. 3: Standard Fourier-transform infrared spectrum of omeprazole magnesium (reference)

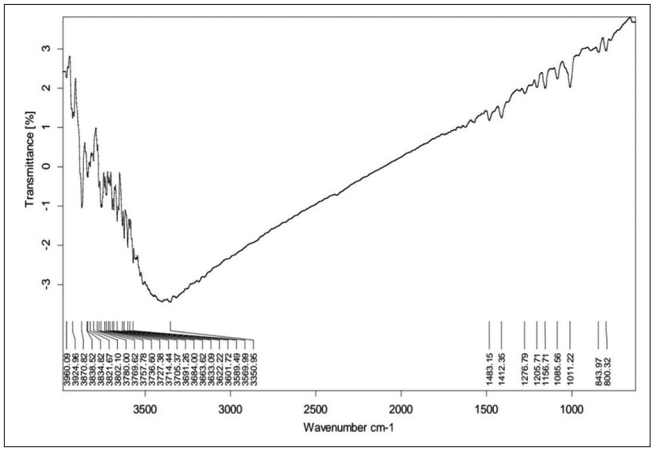

Fig. 4: Fourier-transform infrared of omeprazole magnesium (test)

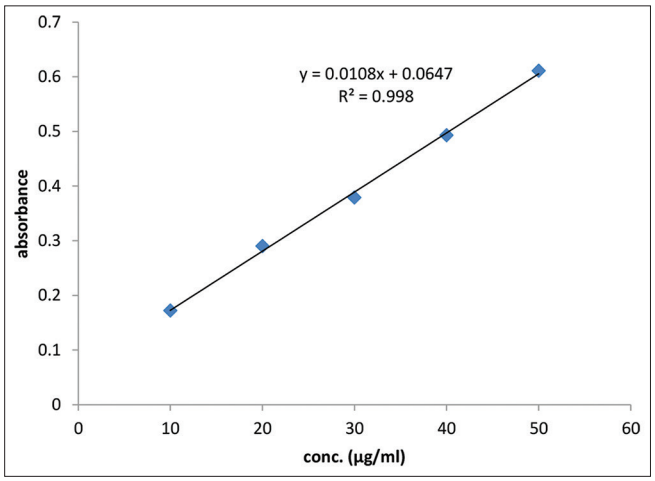

Fig. 5: Calibration curve of omeprazole magnesium

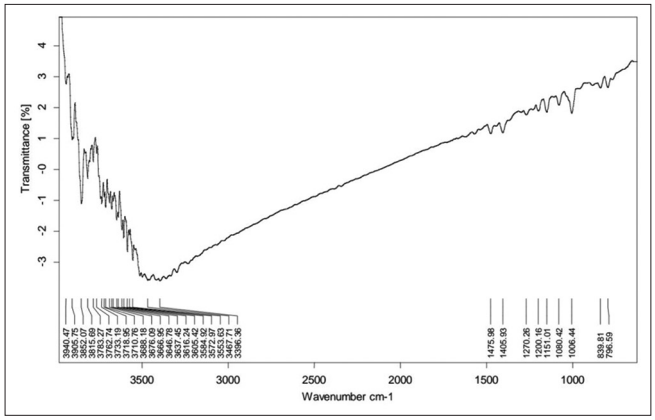

Fig. 6: Fourier-transform infrared spectrum of omeprazole magnesium (immediate)

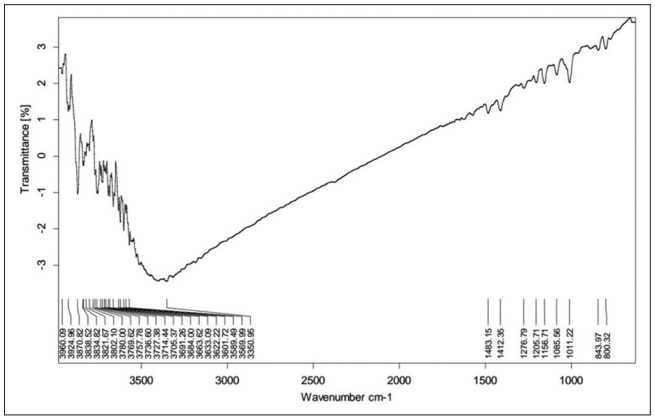

Fig. 7: Fourier-transform infrared spectrum of omeprazole magnesium (after 15 days)

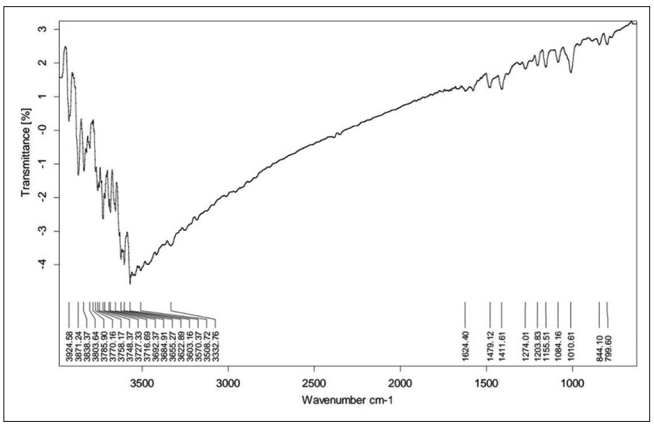

Fig. 8: Fourier-transform infrared spectrum of omeprazole magnesium with sodium alginate (immediate)

***In vitro* drug release study**

The dissolution profile is presented in Table 8 given below. The rate release profile was plotted as the percentage linear drug release versus time. This showed that drug releases increases with increase in time. The dissolution data obtained were plotted as cumulative percentage release versus time.

It was observed that F3 and F6 showed higher release and both were again reformulated and evaluated in the similar manner and it was found that F6 was better in terms of drug release and stability, so, it was

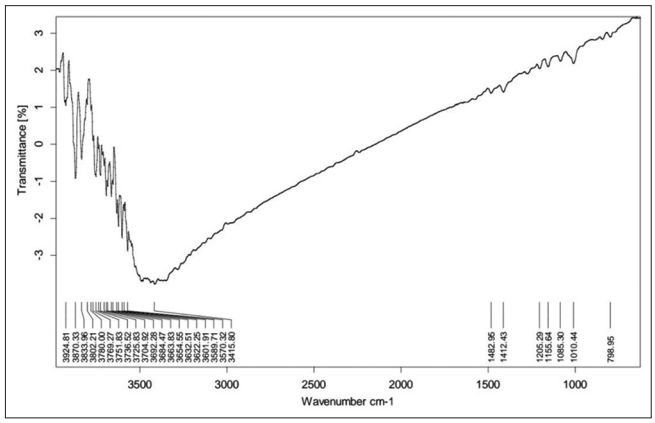

Fig. 9: Fourier-transform infrared spectrum of omeprazole magnesium with sodium alginate (after 15 days)

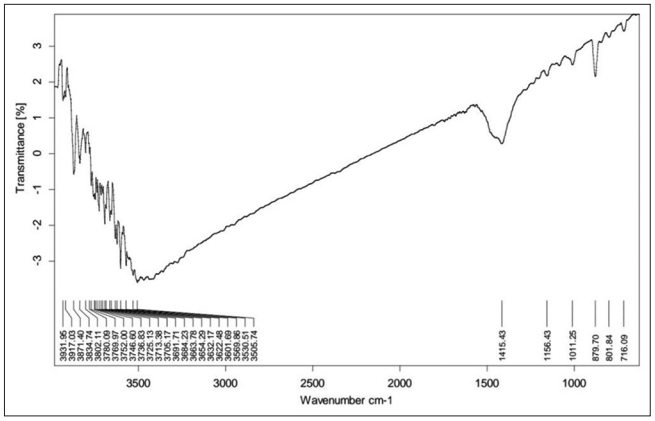

Fig. 10: Fourier-transform infrared spectrum of omeprazole magnesium with calcium carbonate (immediate)

Table 5: Absorbance of omeprazole magnesium

Conc. (mcg/ml)	Abs* (avg.)
10	0.172
20	0.290
30	0.379
40	0.493
50	0.611

*Average of three readings

Table 6: Quantity used for drug and polymer identification and results

S. No.	API and excipients	Quantity per vial (mg)	No. of Vials		Results (complies or not)
			Initial	50°C After 15 days	
1	Omeprazole magnesium	10	1	1	Complies
2	Omeprazole magnesium and sodium alginate	10	1	1	Complies
3	Omeprazole magnesium and calcium carbonate	10	1	1	Complies

Table 7: Physicochemical properties of all formulation

Formulation code	Color	Homogeneity	pH	Gelling capacity	Floating time (h)	Floating lag time (s)	Drug content
F1	White	+	8±0.5	+	10	8	94.03
F2	White	++	8±0.5	++	11	11	92.04
F3	Off White	++	8±0.5	+++	>12	6	97.30
F4	Off White	+	8±0.5	++	9	8	96.10
F5	White	++	8±0.5	+	>12	7	97.10
F6	Off White	++	8±0.5	+++	>12	6	98.20
F7	White	+	8±0.5	++	10	8	93.60
F8	White	++	8±0.5	++	11	9	93.40
F9	Off White	++	8±0.5	+	11.5	10	92.50

Table 8: Results of *in vitro* drug release study of all formulation

Time (min.)	F1	F2	F3	F4	F5	F6	F7	F8	F9
5	3.96	6.48	3.60	0.72	0.36	9.00	5.04	6.12	7.56
10	11.18	11.56	9.74	3.96	3.24	11.21	7.59	10.11	11.20
15	15.20	13.42	17.35	12.62	10.82	13.79	10.87	15.21	16.10
30	20.69	18.53	19.97	17.01	14.84	18.91	13.81	17.45	18.73
45	23.68	21.88	24.04	22.14	20.68	23.33	17.13	20.43	22.44
60	28.49	28.12	29.57	24.06	23.68	25.98	20.46	24.50	25.44
90	35.49	33.67	34.05	27.08	27.05	30.08	29.57	27.88	32.06
120	38.56	39.61	43.24	31.18	30.79	37.09	32.25	32.35	36.56
150	42.37	42.35	44.92	34.59	33.84	42.33	39.27	37.20	42.16
180	46.92	48.34	48.40	39.46	37.27	48.32	48.12	41.01	44.19
240	48.62	50.76	58.02	48.32	48.27	50.74	53.43	44.47	48.75
300	51.76	51.76	61.22	53.98	52.49	58.93	55.88	48.67	56.93
360	55.28	54.91	65.87	60.03	59.97	65.73	58.70	54.33	63.72
420	59.53	59.53	70.18	66.11	65.70	71.49	62.25	58.58	68.38
480	66.69	68.13	73.08	69.71	71.45	74.39	66.19	63.94	73.79
540	71.73	75.33	77.79	74.40	74.36	79.11	70.50	68.24	82.11
600	76.43	77.89	82.52	77.32	79.07	82.05	75.56	74.00	87.95
660	83.31	82.27	88.72	83.49	86.34	87.53	81.72	78.00	90.94
720	94.56	91.34	97.11	89.34	91.84	98.79	89.71	87.05	94.30

Table 9: Result of drug content (in duplicates)

Formulation code	Marketed		Final	
Drug content (%)	92.10	91.23	97.81	97.92

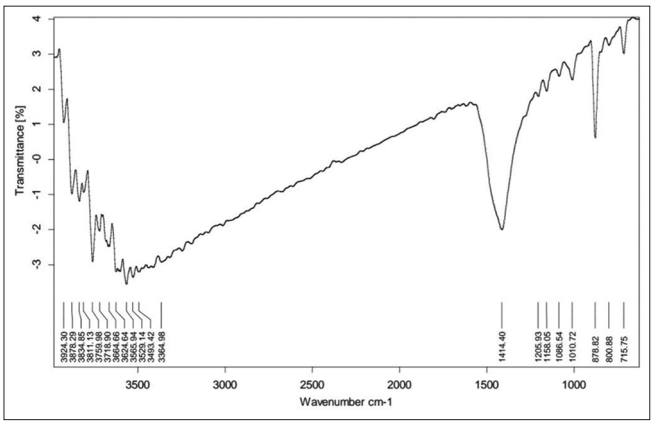

Fig. 11: Fourier-transform infrared spectrum of omeprazole magnesium with calcium carbonate (after 15 days)

selected as the final formulation and compared with available marketed preparation.

Comparative study of final formulation and marketed formulation

Drug content: The drug content observed is as following in Table 9.

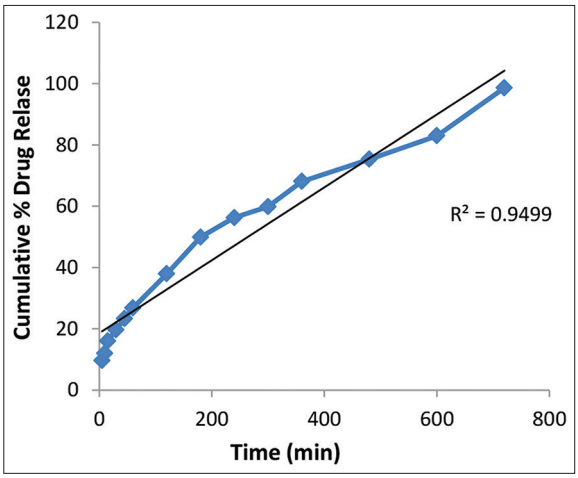

Fig. 12: Zero order equation of final formulation

In vitro drug release

The percentage release versus time value observed for marketed and final formulation in duplicates are mentioned in Table 10.

Kinetic modeling

Model independent Methods: A simple model independent approach uses a difference factor (f1) and a similarity factor (f2) to compare dissolution profiles.

Similarity factor: The result was found to be 51.31. Thus, it complies with the standard value (Table 11).

Table 10: Results of *in vitro* drug release for final and marketed formulation

Time (min)	5	10	15	30	45	60	120	180	240	300	360	480	600	720
Final formulation (%CDR)	3.7	11.94	15.96	19.65	23.31	26.79	37.91	49.88	56.27	59.81	68.05	75.29	82.96	98.63
	3.76	11.93	14.88	19.64	24.79	26.73	37.84	49.80	55.47	59.73	67.25	75.20	82.87	97.82
Marketed (%CDR)	2.91	10.4	24.9	43.1	67.8	89.7								
	3.28	10.9	26.2	43.8	69.12	90.12								

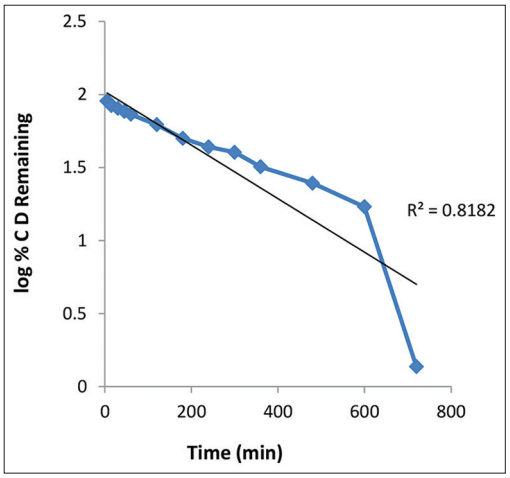

Fig. 13: First order equation of final formulation

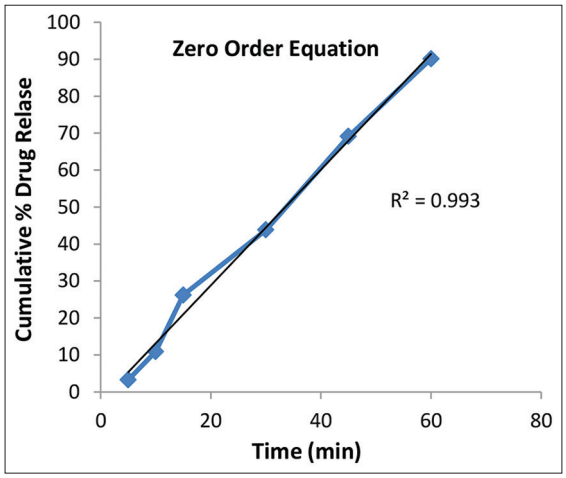

Fig. 16: Zero order equation of marketed formulation

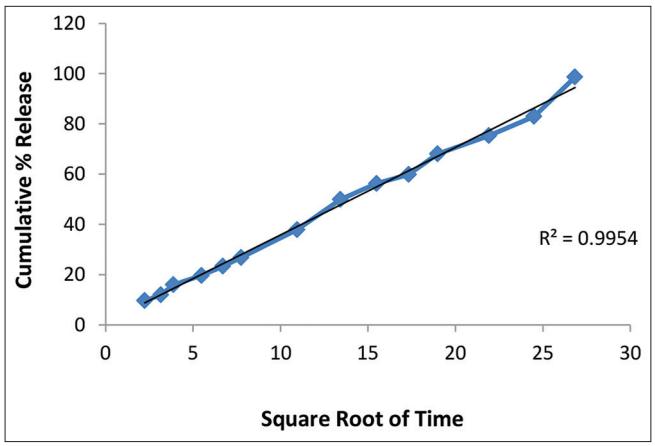

Fig. 14: Higuchi equation of final formulation

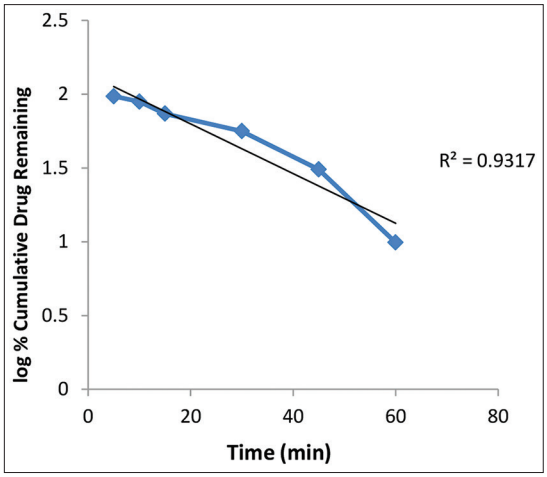

Fig. 17: First order equation of marketed formulation

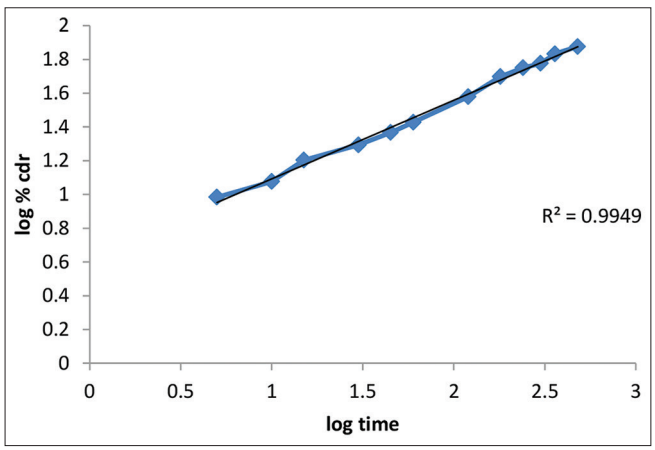

Fig. 15: Korsmeyer–peppas equation of final formulation

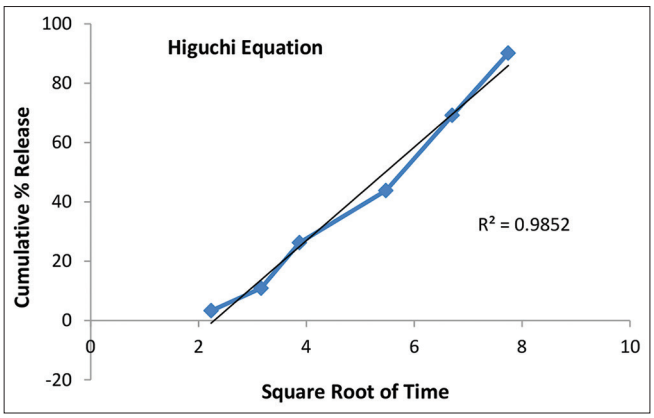

Fig. 18: Higuchi equation of marketed formulation

Table 11: Results of similarity factor

Time (min)	Test	Reference	Reference – Test	log [{1+(Rt-Tt)*1/n}-0.5]*100	50+log [{1+(Rt-Tt)*1/n}-0.5]
5	3.7	3.28	−0.42	1.5569	51.5569
10	11.94	10.9	−1.04	1.9826	51.9826
15	15.96	26.2	10.24	1.5213	51.5213
30	19.65	43.8	24.15	1.1693	51.1693
45	23.31	69.12	45.81	0.8947	50.8947
60	26.79	90.12	63.33	0.7547	50.7547
Average					51.31

Table 12: Results of difference factor

Time (min)	R	T	∑(R-T)	∑ R	∑(R-T)/ ∑ R	∑(R-T)/ ∑ R*100
5	3.28	3.7	−0.42	3.28	−1.1280	−112.8049
10	10.9	11.94	−1.46	14.18	−0.1030	−10.2962
15	26.2	15.96	9.2	37.1	0.2480	24.7978
30	43.8	19.65	34.39	70	0.4913	49.1286
45	69.12	23.31	69.96	112.92	0.6196	61.9554
60	90.12	26.79	109.14	159.24	0.6854	68.5381
Average						13.55

Table 13: Release kinetics of final formulation

Time (min)	Sq.rt time	Log time	%cdr	log %cdr	log % cdr remaining
5	2.2361	0.6990	9.63	0.9836	1.9560
10	3.1623	1.0000	11.94	1.0770	1.9448
15	3.8730	1.1761	15.96	1.2030	1.9245
30	5.4772	1.4771	19.65	1.2934	1.9050
45	6.7082	1.6532	23.31	1.3675	1.8847
60	7.7460	1.7782	26.79	1.4280	1.8646
120	10.9545	2.0792	37.91	1.5788	1.7930
180	13.4164	2.2553	49.88	1.6979	1.7000
240	15.4919	2.3802	56.27	1.7503	1.6408
300	17.3205	2.4771	59.81	1.7768	1.6041
360	18.9737	2.5563	68.05	1.8328	1.5045
480	21.9089	2.6812	75.29	1.8767	1.3929
600	24.4949	2.7782	82.96	1.9189	1.2315
720	26.8328	2.8573	98.63	1.9940	0.1367

Table 14: Release kinetics of marketed formulation

Time (min)	Sq.rt time	log time	%cdr	log % cdr	log %cdr remaining
5	2.2361	0.6990	3.28	0.5159	1.9855
10	3.1623	1.0000	10.9	1.0374	1.9499
15	3.8730	1.1761	26.2	1.4183	1.8681
30	5.4772	1.4771	43.8	1.6415	1.7497
45	6.7082	1.6532	69.12	1.8396	1.4897
60	7.7460	1.7782	90.12	1.9548	0.9948

Table 15: R^2 values of different models for final formulation and marketed formulation

Formulation	Model	R^2 value
Final	Zero order	0.949
	First order	0.818
	Higuchi equation	0.995
	Korsmeyer-Peppas	0.994
Marketed	Zero order	0.933
	First order	0.931
	Higuchi equation	0.985
	Korsmeyer-Peppas	0.967

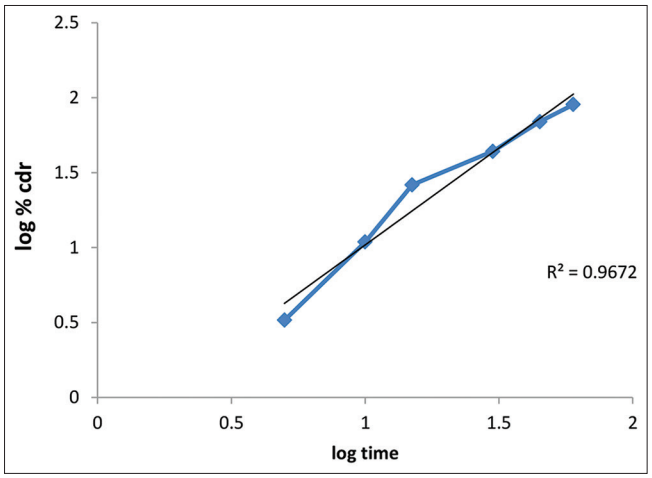

Fig. 19: Korsmeyer–Peppas equation of marketed formulation

Difference factor

It was found to be 13.55. Thus, it complies with the standard value (Table 12).

Model dependent methods

The dissolution profiles were evaluated depending on the derived model parameters. The model dependent approach included zero order, first order, Higuchi, and Korsmeyer–Peppas model, etc.

Release kinetics

Release kinetics described the overall release of the drug from the dosage forms. Release kinetics of both final formulation and marketed product was determined using different mathematical models as shown in Tables 13 and 14. In case of zero order ($Q_t = Q_o + K_o t$). The graph was plotted in cumulative percentage release versus time and in first order release kinetic ($\log C = \log C_o - Kt/2.303$). The graph was plotted in log cumulative percentage of drug remaining versus time. For Higuchi model kinetics ($Q = K_H \times t^{1/2}$), the graph was plotted in cumulative percentage of drug versus square root of time and for the Korsmeyer-Peppas ($Q/Q_o = Kt^n$) model, the graph was plotted in log cumulative percentage of drug released versus log time.

These are graphically enlisted below (Figs. 5-19):

1. Final formulation
   - Zero order equation
   - First order equation
   - Higuchi equation
   - Korsmeyer-Peppas equation

2. Marketed formulation
   - Zero order equation
   - First order equation
   - Higuchi equation
   - Korsmeyer-Peppas equation

Final formulation complies with marketed formulation for its release pattern, that is, Higuchi equation (Table 15).

CONCLUSION

The present work was carried out to develop a novel gel based *in situ* drug delivery system of omeprazole magnesium. The methodology adopted for preparation of *in situ* gel solution was very simple and cost effective. It is newer approach to improve easy instillation, residence time and bioavailability and prolong drug release. Nine formulation batches were prepared and subjected for evaluation, namely, floating lag time and *in vitro* drug release. Results showed that F3 and F6 gave good results for *in vitro* drug release and floating lag time. Among all the formulation, the F3 and F6 were best formulations. From these two formulations, the best was selected on the behalf of their respective evaluation parameter. F3 and F6 formulations were again formulated and evaluated. Results showed that F6 formulation gives best results. So, F6 was found to be the best candidate for further study. F6 formulation was evaluated for all parameters, namely, homogeneity, pH, color, floating lag time, floating time, *in vitro* drug release, and drug content. All the parameters were found to be within the limits. F6 formulation was then compared with the available marketed formulation, that is, OMEZ Insta 20 mg by Dr. Reddy's. Comparison was made in respects, that is, drug content, *in vitro* drug release. Kinetic modeling was done between both the formulations with respect to model dependent and model independent kinetics. Final formulation complies with marketed formulation for its release pattern, that is, Higuchi equation. Results showed that *in situ* gel has good floating lag time and floating time that is an essential factor for *in situ* gel. *In vitro* drug release was found optimum. The f1 value was 13.55 (similarity or equivalence of two profiles) and f2 value was 51.31 (dissolution profiles are somewhat identical). The developed formulation is a viable alternative conventional solution by virtue of its ability to enhance bioavailability through its longer gastric residence time and ability to sustain drug release as well as the advantage of floating and pH which minimize the degradation of omeprazole magnesium which is easily degraded by acidic environment.

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AUTHORS CONTRIBUTIONS

All the authors contributed to the preparation of the final manuscript.

CONFLICT OF INTEREST

No conflict of interest.

AUTHORS FUNDING

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