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Formulation and evaluation of omeprazole nanoparticles by using natural polymers

Sirisha Mittapally and Arifa Banu

Abstract
Nanoparticles are solid colloidal particles having size range from 10 to 1000 nm (nanometer). The polymeric materials are used as a carrier for the controlled drug delivery. These nanoparticles were prepared by the desolvation method by using the natural polymers gelatin and sodium alginate as they are biodegradable and biocompatible.
The nanoparticles of gelatin 5% with different concentration of sodium alginate ranges from (1-6%) were evaluated for enteric coating. These nanoparticles are used to formulating tablet dosage form using aluminum hydroxide as diluent. The prepared tablets were evaluated for pre compression and post compression properties. Among all the formulations dissolution studies showed that f4 formulation containing 5% gelatin and 4% sodium alginate has enteric coating as well as controlled release property and releases 2.49% of drug in acidic PH (1.2) and 98% of drug in intestinal PH (6.8). Gelatin forms the nanoparticles and sodium alginate forms a polymer matrix there by releases the drug in a controlled manner. Stability and accelerated stability studies of the omeprazole USP tablets shown that the f4 formulation has the promising result with 98% drug release within 12 hours in intestinal PH.

Keywords: Nanoparticles, gelatin, sodium alginate, enteric coating

1. Introduction
Nanoparticles are solid colloidal particles having size range from 10 to 1000 nm (nanometer) [5, 10]. Polymers are used for controlled release of drug in the preparation of nanoparticles. Synthetic as well as natural polymers were used. Natural polymers have an advantage of biodegradability and compatibility over synthetic polymers. The first nanoparticles were based on non-biodegradable polymeric systems (polyacrylamide, polymethyl methacrylate, polystyrene etc.).
Sustained or controlled release of drug, from the nanoparticles are achieved with the help of polymer which are the sub micronic colloidal carriers, hence have higher stability when in contact with biological fluids and protect the active ingredients from enzymatic action and enhance its absorption from the site of action.

2. Materials and Methods
Gelatin nanoparticles were prepared using a desolvation technique. Gelatin (1.25 g) was dissolved in distilled water (25 ml) under constant heating temperature, accurately weighed quantity of omeprazole USP and sodium alginate added slowly. Acetone (25 ml) was added to the above solution as a desolvating agent to precipitate the high molecular weight (HMW) gelatin. The supernatant was discarded and the HMW gelatin re-dissolved by adding 25 ml distilled water and stirring at 600 rpm under constant heating 50-60 ºC. Acetone (75 ml) was added drop-wise to form nanoparticles. Later 25% glutaraldehyde solution (250 µl) was used as a cross-linking agent, and stirred for about 5 hour at 600 rpm. The acetone was evaporated using concentrator (speed vacuum). The resultant nanoparticles were stored at 2-8 °C [7].
The enteric coated nanoparticles tablet were prepared with aluminium hydroxide as diluent by direct compression method using optimum concentration of glidant and lubricants.
The formulations F1 to F6 were prepared using varying concentration of sodium alginate as given below.

Table 1: List of materials

S. No	Ingredients	Category	Manufacturer
1	Omeprazole	Anti-ulcer	Bindu Pharmaceutical, Hyderabad, India.
2.	Gelatin	Polymer	Sd fine chem. Ltd
3.	Sodium alginate	polymer &enteric coating	Sd fine chem. Ltd
4.	Aluminium Hydroxide	Antiulcer &Excipient	Moly chem. Mumbai, India.
5.	Magnesium stearate	Lubricant	Merck specialities pvt. Ltd, Mumbai, India.
6.	Talc	Lubricant	Merck specialities pvt. Ltd, Mumbai, India.
7.	Methanol	Solvent	Fine chemical co., Ltd
8.	Distilled water	Solvent	Stangen fine chemical Hyderabad.
9.	Acetone	Desolvating agent	Fischer
10.	25% Glutaraldehyde	Cross linking agent	Sd fine chem. Ltd

Table 2: Formulation of enteric coated omeprazole nanoparticles tablet

INGRDIENTS	F1	F2	F3	F4	F5	F6	ROLE
Omeprazole (mg)	20	20	20	20	20	20	Drug
Gelatin (%)	5	5	5	5	5	5	Rate controlling natural polymer
Sodium alginate (%)	1	2	3	4	5	6	Rate controlling natural polymer & enteric coating
Glutaraldehyde 25% (drops)	2-3	2-3	2-3	2-3	2-3	2-3	Cross linking agent
Aluminium hydroxide	Q.S.	Q. S.	Q. S.	Q. S.	Q. S.	Q. S.	Drug andexcipient
Acetone (ml)	70	70	70	70	70	70	Desolvating agent
Talc	Q.S.	Q. S.	Q. S.	Q. S.	Q. S.	Q. S.	Glidant
Magnesium stearate	Q. S.	Q. S.	Q. S.	Q. S.	Q.S.	Q. S.	Lubricant
Total w t (mg)	150	150	150	150	150	150	

3. Results and Discussion

3.1 Standard graph of USP omeprazole using methanol

Standard graph of USP omeprazole were prepared by using methanol as solvent and measured the absorbance at 302nm and draw the graph by taking concentration on x- axis and absorbance on y- axis [29].

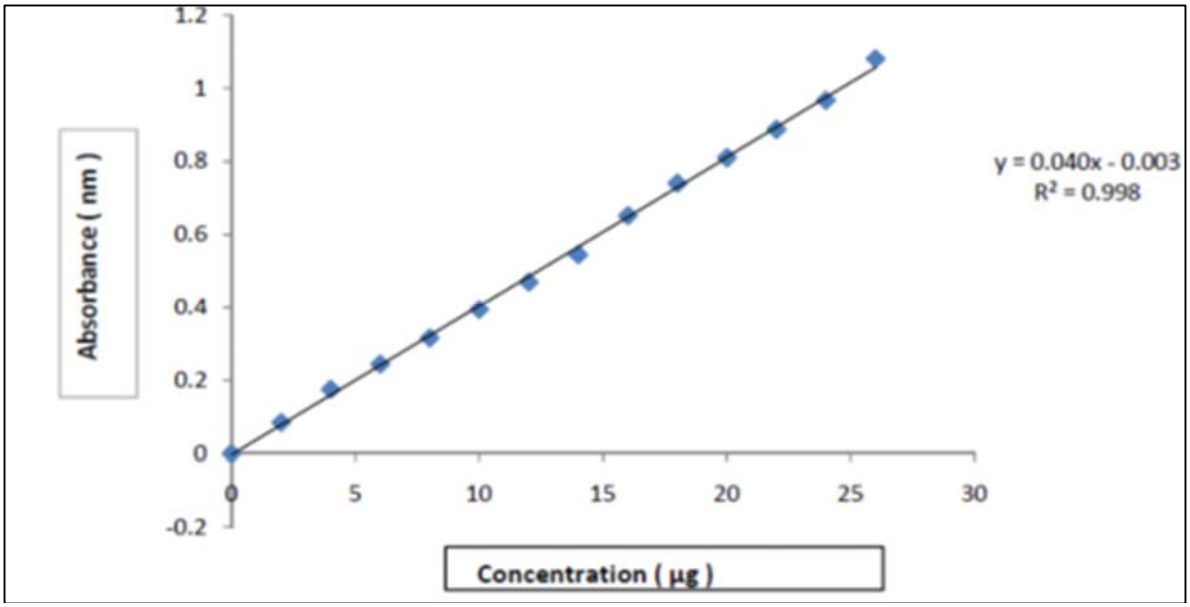

Fig 1: Calibration curve of omeprazole

3.2 Drug excipient compatibility studies

The FT-IR spectrum shows characteristic peaks corresponding to various functional groups present in Omeprazole structure. Various functional groups and their respective peaks were identical to the reference spectra given in Japanese Pharmacopeia which proves purity of test sample of Omeprazole [6].

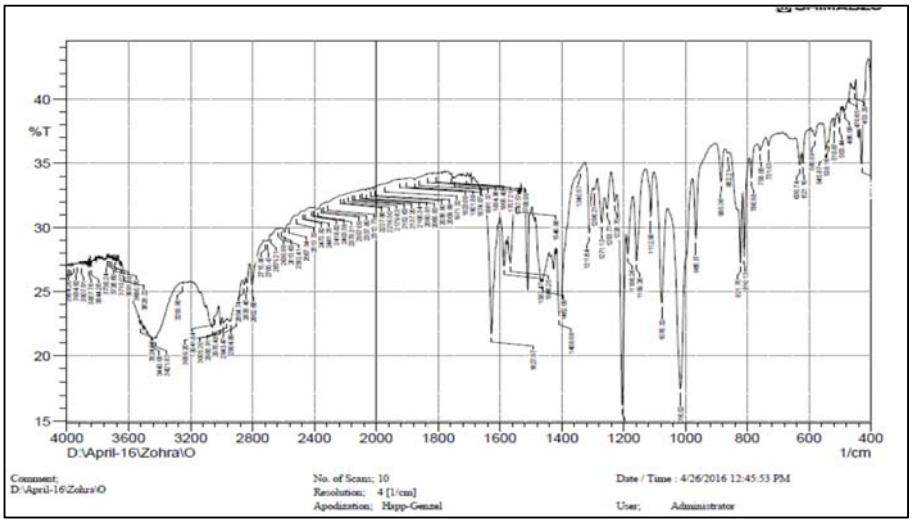

Fig 2: FT-IR spectra of omeprazole pure drug

Sample A (omeprazole + aluminium hydroxide)

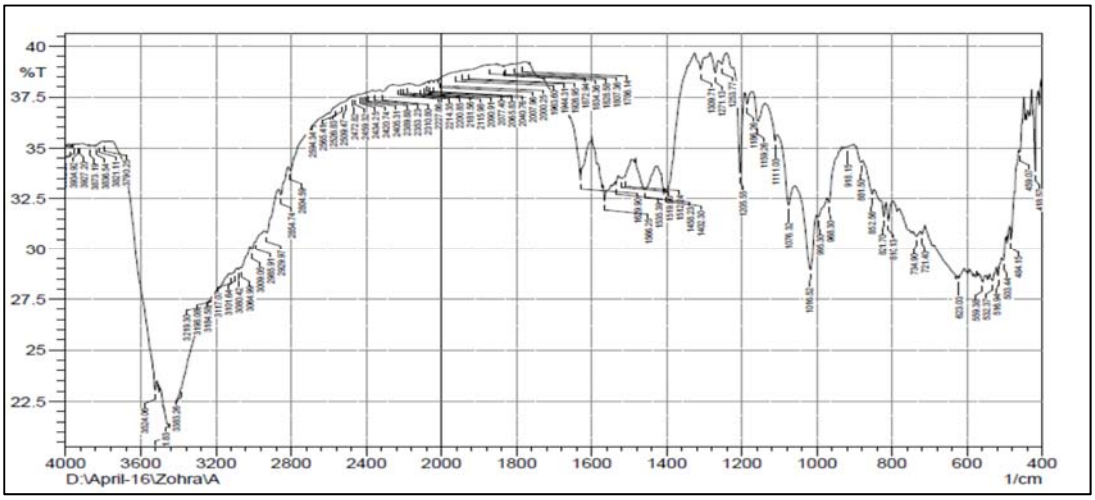

Fig 3: FT-IR spectra of sample A

Sample B (omeprazole + gelatin)

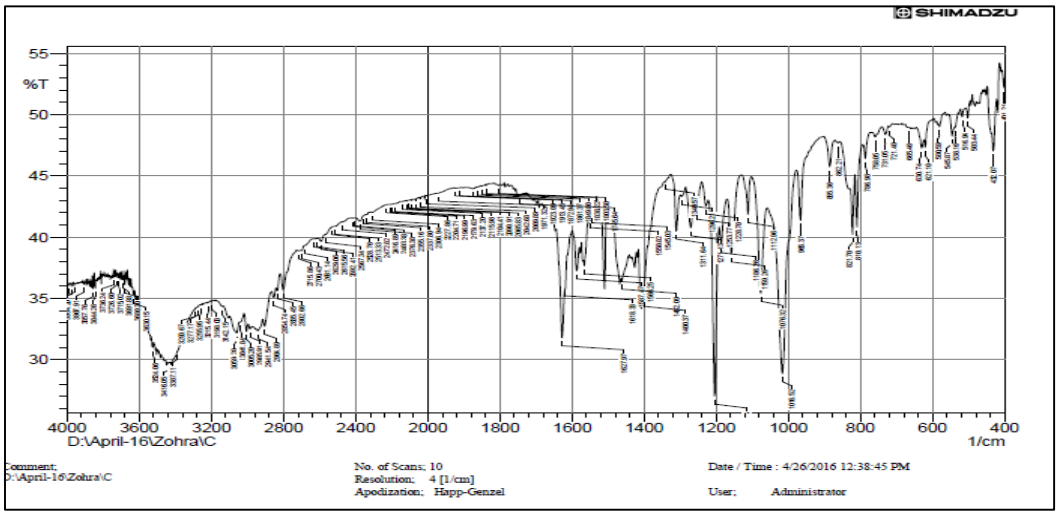

Fig 4: FTIR spectra of sample B

Interpretation of FTIR Spectra of Sample B

Table 3.4: FTIR spectra of sample B

Functional Group	Frequency (cm^{-1})	Functional Group	Frequency (cm^{-1})
N-H	3524.06	C-N	1550.82

The FTIR spectra have shown that all the functional groups are protected in sample A & B and found that there is no incompatibility between the drug and excipients.

3.3 Pre compression studies

Table 3: Pre Compression Studies of enteric coated omeprazole nanoparticles tablet

Parameters	Enteric Coated Nanoparticles Tablet				
	F1	F2	F3	F4	F5
Bulk density (gm/ml)	0.48	0.49	0.48	0.51	0.48
Tapped density (gm/ml)	0.58	0.60	0.57	0.62	0.60
Carr's index (%)	17	18.12	15.2	17.39	16
Hausner's ratio	1.20	1.22	1.18	1.20	1.22
Angle of repose (θ)	35^0	36^0	39^0	35^0	37^0
Porosity	0.17	0.18	0.19	0.15	0.17

The preliminary batches F1 to F5 showed the angle of repose 35º to 37º and Hausner's ratio between 1.20 to 1.22 which indicates good flow property and compressibility of all the preliminary batches.

3.4 Post compression studies

Weight variation, Hardness, Friability, Thickness, Content uniformity [1, 6]

Table 4: Post Compression Studies of enteric coated nanoparticles tablet

Formulation code	Weight variation	Hardness (kg/cm^2)	Friability (%)	Thickness (mm)	Content uniformity (%)	Disintegration Time (min)
F1	150	4.5	0.72	2.6	99.28	3.15
F2	149	4.3	0.68	2.6	97.16	4
F3	148	5	0.69	2.7	96.10	10
F4	151	5.6	0.66	2.75	99.68	8
F5	151	5.7	0.68	2.6	99.19	15
Acceptance criteria	185-215	4-8	<1	-	90-110	

All the post compression parameters are found within the limits, in this F4 was found to be good formulation.

3.5 *In vitro* drug release of nanoparticles tablet pH (1.2)

Table 5: *In vitro* Drug Release Study PH (1.2)

Time(min)	F1 (%)	F2 (%)	F3 (%)	F4 (%)	F5 (%)
30	6.8	2.3	2.1	1.68	1.7
45	17.4	6.2	4	1.7	3
60	20.6	15.3	8.8	1.9	7
90	28	25.6	6	2.2	12.9
120	40	30	21	2.45	15

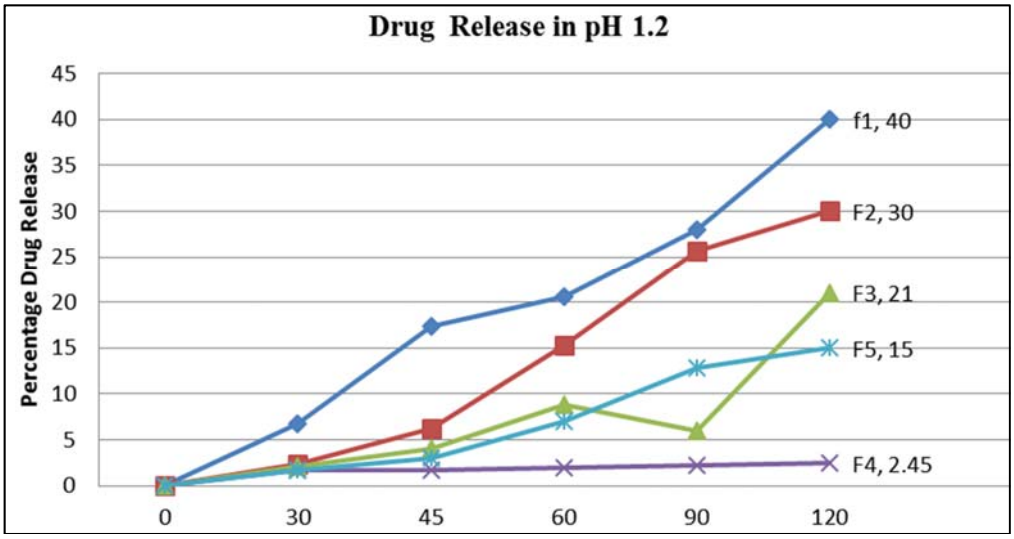

Fig 5: *In –Vitro* Drug Release Study PH (1.2)

3.6 *In vitro* drug release of nanoparticles tablet in pH (6.8)

Table 6: *In vitro* Drug Release Study pH (6.8) [1]

Time (min)	F1 (%)	F2 (%)	F3 (%)	F4 (%)	F5 (%)
4	18	20	21	30	15
6	32	40	41	44	30
8	41	52	56	63	44
10	48	62	62	86	58
12	59	70	88	98	69

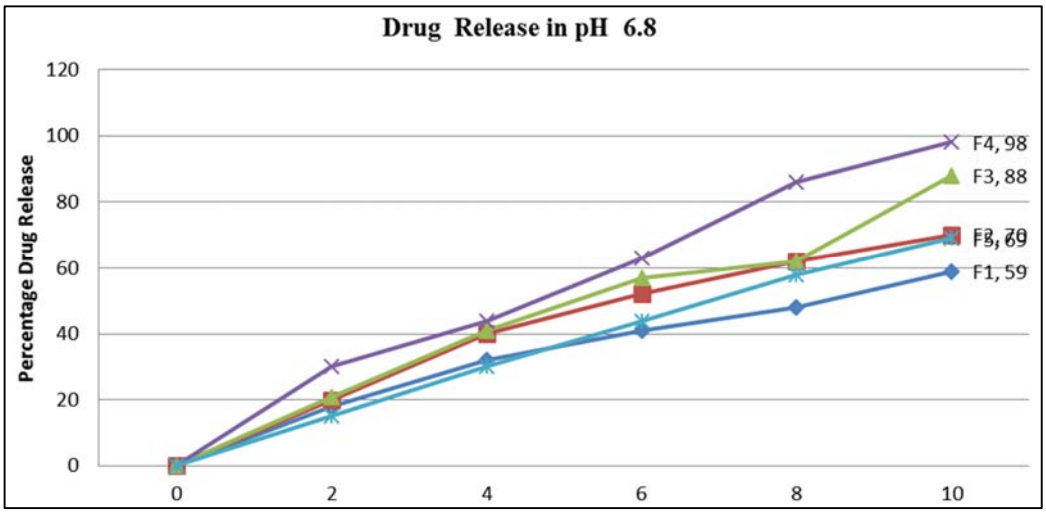

Fig 6: *In vitro* Drug Release Study pH (6.8)

3.7 Kinetic study of optimized formulation (f4)

Table 7: kinetic study

Zero	Higuchi	Peppas	First	Hixson Crowell
1	2	3	4	5
R (cvt)	R (cvroot (T))	Log T vs Log C	Time vs log % remaining	Time vs q1/3qt1/3)
8.400	27.451	1.118	-0.015	0.271
0.9965	0.9402	0.9968	-0.8772	0.9434
0.9931	0.8839	0.9937	0.7695	0.8900

From the above information it was concluded that the following F4 optimised formulation follow the zero order kinetics and peppas model which reveals that the mechanism of drug release from the formulation is by diffusion, erosion, swelling and may be the combination of diffusion and swelling, Greater the regression coefficient greater the linearity towards the kinetic model.

3.8 Stability studies of enteric coated omeprazole nanoparticles tablet of optimized formulation

Stability study of enteric coated omeprazole nanoparticles tablet was carried out for 4 weeks at specified condition. From the stability studies it was revealed that there is no significant changes in the physical parameters, disintegration time, % drug content and % drug release at 180 min in phosphate buffer pH 6.8 when stored at temperature and humidity conditions of 25 ºC ±2C / 60% RH ± 5% RH and 40 ± 2 ºC/ 75% RH ± 5% RH. So, It can be concluded that f4 formulation having good stability [1, 6].

Table 8: Long term stability studies of optimized formulation

Evaluation Parameters	Long Term 25 ^{0}C/60% RH			
Sampling Interval Days	0	15	30	90
Wt variation	0	0	0	0
Hardness	4.5	5	5.5	4.8
Friability	0.68	0.72	0.66	0.62
Thickness	2.54	2.54	2.54	2.54
Content uniformity	99.76	99.76	99.5	99.5

Table 9: Intermediate stability studies of optimized formulation

Evaluation Parameters	Intermediate 30 ^{0}c/65% Rh			
Sampling Interval Days	0	15	30	90
Wt variation	0	0	0	0
Hardness	4.5	5.2	4.8	5
Friability	0.64	0.68	0.7	0.64
Thickness	2.54	2.54	2.54	2.54
Content uniformity	99.76	99.76	99.3	99.3

Table 10: Accelerated stability studies of optimized formulation

Evaluation Parameters	Accelerated 40 ^{0}C/75% Rh			
Sampling Interval Days	0	15	30	90
Wt variation	0	0	0	0
Hardness	4.6	5.2	5	5
Friability	0.66	0.63	0.71	0.69
Thickness	2.54	2.54	2.54	2.54
Content uniformity	99.76	99.2	99	99

Table XI: Stability Studies for F4 formulation

Percentage Drug Release			
Sampling interval	**25 ^{0}C/60% RH**	**30 ^{0}C/65% RH**	**40 ^{0}C/75% RH**
0 Days	98	98	98
15 Days	98	98	97.6
30 Days	97.8	97.72	97
90 Days	97.5	97.44	96.8

Stability studies of optimized formulation F4 were carried out to determine the effect of formulation additives on the stability of the drug and also to determine the physical stability of the formulation. The stability studies were carried out at 25 ^{O}C/60% RH, 30 ºC/65% RH and 40 ºC/75% RH for 90 days. There were no significant changes in the physical property and percent of drug release and results was found within the limits ±4 during 12 hour of stability period.

4. Conclusion

The present study demonstrates that omeprazole enteric coated nanoparticles tablets were prepared using enteric coating polymers such as gelatin and sodium alginate. Omeprazole and excipients were compatible with each other as indicated by FT-IR. Among the different formulations prepared in this study, batch F4 containing 4% sodium alginate and 5% gelatinhas shown negligible drug release in 0.1 N HCl and after 12 hours in phosphate buffer showed 98% drug release and from the kinetic study, F4 optimized formulation follow the zero order kinetics i.e. independent of concentration and peppasmodel which reveals that the mechanism of drug release from the formulation is by diffusion, erosion swelling and may be the combination of diffusion and swelling. Stability studies were found within the limit. So F4 was good formulation as it was meeting all specifications. The results demonstrated the effective use of enteric coated omeprazole nanoparticle tablets as a controlled release preparation for treatment of duodenal ulcer.

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