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Journal of Chemical and Pharmaceutical Research, 2014, 6(7):82-89

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Formulation and evaluation of clarithromycin gastroretentive dosage form

Dheeraj L. Patingrao and Pramod Kadu*

Department of Pharmaceutics, Dr Bhanuben Nanavati College of Pharmacy, Vile Parle, Mumbai, India

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ABSTRACT

Floating matrix tablets of clarithromycin were developed to prolonged gastric residence time and thereby increase drug availability. The tablets were formulated by wet granulation technique, using polymers such as Guar Gum, HPMC-K15M and HPMC-K100M, and other standard excipient. Tablets were evaluated for physical characteristics viz, hardness, percentage friability, floating capacity, weight variation and content uniformity. Further, tablets were evaluated for in-vitro release characteristics for 12hr. Increasing the polymer ratio the FLT was increase but the drug release was decreased.

Keywords: Clarithromycin, Guar Gum, Gasto Retentive Tablets.

INTRODUCTION

Clarithromycin is a macrolide antibiotic widely recommended in H.pylori mediated peptic ulcers, Upper Respiratory Tract Infections (1).The prescribed adult oral dosage of clarithromycin is 500 mg twice daily for the effective medication of H.pylori caused peptic ulcer. As the drug is effective when the plasma fluctuations are minimized, sustained release formulation of clarithromycin is desirable. The short biological half life of drug (~3–5 h) (2) also favors development of sustained release formulation.

A traditional oral sustained release formulation of clarithromycin may not be useful in the elimination of H. pylori, because the organism lives deep inside the gastric mucosa; also the oral bioavailability of clarithromycin is 55%. Thus it is a sensible way to improve the therapeutic efficacy of the antibiotic if the gastric residence time of the dosage form is increased in the ecological niche of bacterium. The high concentrations of antibiotic clarithromycin in the stomach will ensure effective localized treatment for the pathogen (3). This makes the necessary for the development of gastro retentive dosage forms of clarithromycin. Several approaches are presently used to prolong gastric retention time. These include floating drug delivery systems, also known as hydrodynamically balanced systems, swelling and expanding systems, polymeric bioadhesive systems, modified-shape systems, high density systems and other delayed gastric emptying devices (4). The basis of buoyant preparation offers a simple and practical approach to achieve increased gastric residence time for the dosage form and sustained drug release.
In context of the above principles, a strong demand was recognized for the development of a dosage form to deliver clarithromycin in the stomach and to increase the efficiency of the drug, giving sustained action. The present investigation applied a systematic approach to the development of gastro retentive Clarithromycin dosage forms.

MATERIALS AND METHODS

Materials:

Clarithromycin was received as gift sample from Micro labs, Powai, Mumbai. HPMC K15M (nominal viscosity of 2% aqueous solution 15000 cPs), HPMC K100M (nominal viscosity of 2% aqueous solution 130000 cPs), Guar Gum, Avicel PH102, PVP K-30, Sodium bicarbonate, Mg-stearate, Talc were procured from SD Fines chemicals Private Ltd., Mumbai, India. All other ingredients were of laboratory grade.

Methods:

PREPARATION OF STANDARD CURVE OF CLARITHROMYCIN:

The samples of different concentration were analyzed at 272 nm using UV-VISIBLE spectrophotometer against 0.1N HCL pH 1.2 as blank.

Fig.1: Calibration Curve Of Clarithromycin

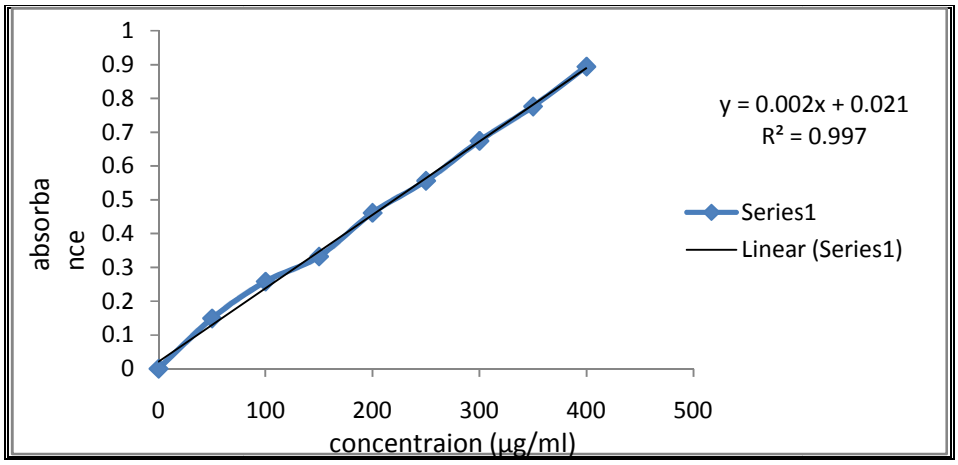
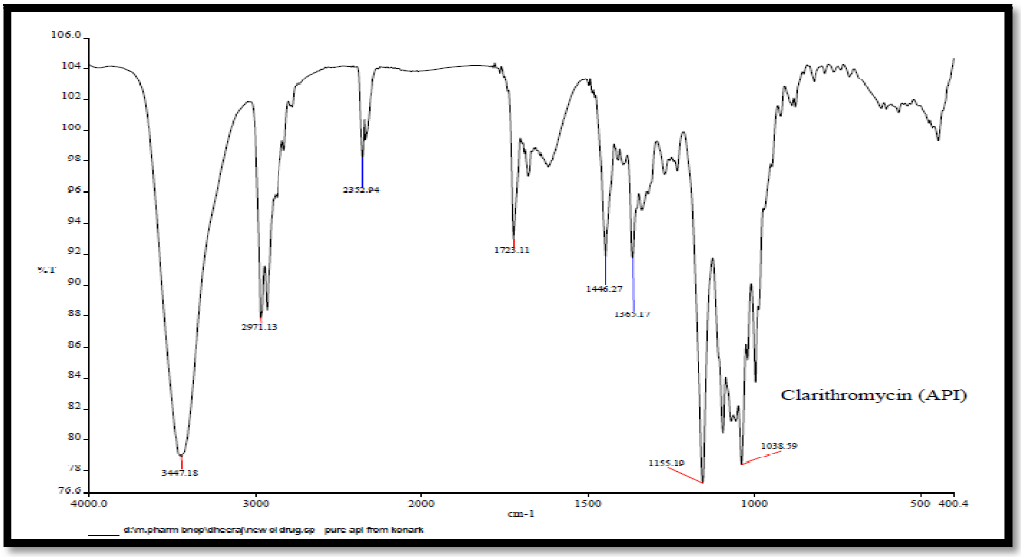


Fig.2: FTIR of Pure Drug

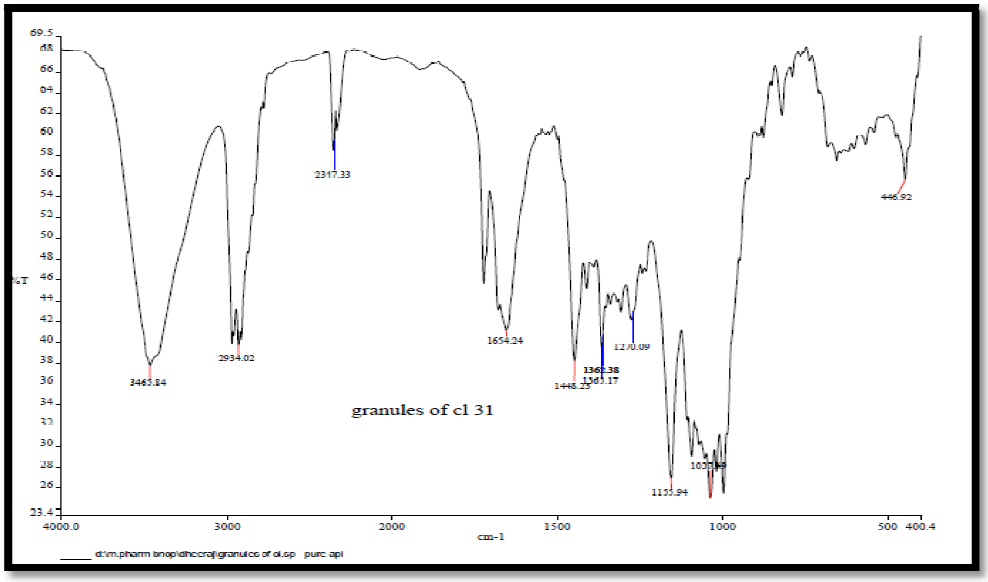


DRUG POLYMER COMPATIBILITY STUDIES:

Drug polymer interaction was studied by FTIR spectroscopy. The spectra were recorded for pure Clarithromycin and with polymer mixture. Drug- polymer interactions were studied by FTIR spectroscopy. The spectra were recorded for Clarithromycin, physical mixture of polymers and physical mixture of drug with polymers using FTIR

– spectrophotometer (FTIR 8400S; SHIMADZU, Japan) from KBr pellets. The scanning range was 400-4000cm-1 and the resolution was 1 cm-1.

Fig.3: Drug Polymer Compatibility Studies By Ftir



FORMULATION DEVELOPMENT:

Floating matrix tablets containing clarithromycin were prepared by wet Granulation technique using varying concentrations of different grades of polymers with sodium bicarbonate. Polymers and clarithromycin were mixed homogeneously using glass mortar and pestle. Isopropyl alcohol was used as granulating agent. Granules were prepared by passing the wet coherent mass through a # 16 sieve. The granules were dried in hot air oven at a temperature of 60°C. Dried granules were sieved through # 20/44 sieves and mixed with sodium bicarbonate used as gas generating agent and lubricated with magnesium stearate and talc just 4-5 min before compression. Lubricated granules were compressed into tablets using Krishna Minipress-I rotary tablet machine to obtain tablets of desired.

Table.1: Formulation Chart Of Developed Gastroretentive Tablets

INGREDIENTS	A	B	C	D	E	F
CLARITHROMYCIN	250	250	250	250	250	250
HPMC K15M	110	-	100	180	-	-
HPMC K100M	-	100	100	-	170	-
GUAR GUM	50	50	-	-	-	154
PVP K-30	70	70	70	70	70	70
AVICEL PH-102	130	140	90	110	120	136
SODIUM CARBONATE	75	75	75	75	75	75
TALC	10	10	10	10	10	10
MAGNESIUM STREATE	5	5	5	5	5	5
Total	700	700	700	700	700	700

EVALUATION OF GASTRO RETENTIVE CLARITHROMYCIN TABLETS:

Evaluation was performed to assess the physiochemical properties and release characteristics of developed formulation.

PRECOMPRESSION PARAMETERS:

ANGLE OF REPOSE (5)**:**

The powder was allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of granules formed.

$$\text{Tan } \varphi = h/r$$

Therefore, φ= Tan-1 h/r
Where, φ = angle of repose, h = height of the cone, r = radius of the cone base
Where φ- Angle of repose, h- height and r- radius

The relationship between angle of repose and powder flow is as follows in given table.

Table.2: Standard Value Of Powder Flow Property Test

Sr.No	Angle of Repose	Powder Flow
1	<25	Excellent
2	25-30	Good
3	30-40	Passable
4	40	Very poor

BULK DENSITY:
Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity of 5 g of powder from each formulation was introduced into a 10 ml measuring cylinder. Initial volume was observed, the cylinder was allowed to tap. The tapping was continued until no further change in volume was noted. Bulk density is calculated by using formula:

Bulk density (ρb) = Bulk volume of the powder/Weight of the powder
Tapped density (ρt) = Tapped volume of the powder/ Weight of the powder

CARR'S INDEX (6)**:**
The Carr's index of the powder was determined by using formula:
Carr's index (%) = [(TBD -LBD) × 100]/TBD
Where, LBD = weight of the powder/volume of the packing
TBD = weight of the powder/tapped volume of the packing

Table.3: Standard Value Of Powder Carr's Index Test

Sr.No	Carr's index	**Type of flow**
1	5-15	Excellent
2	12-18	Good
3	18-23	Satisfactory
4	23-35	poor
5	>40	Very poor
6		Extremely poor

POST COMPRESSION PARAMETERS:
TABLET THICKNESS:
Thickness and was measured using a calibrated screw gauge. Three tablets of each formulation were picked randomly and thickness was measured individually.

HARDNESS:
Hardness indicates the ability of a tablet to withstand mechanical shocks while handling the hardness of the tablets was determined using Pfizer hardness tester. It is expressed in kg/cm^2. Three tablets were randomly picked and hardness of the tablets was determined.

FRIABILITY:
Roche friabilator was used for testing the friability. Twenty tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm. After 4 min., the tablets were weighed and the percentage loss in tablet weight was determined.

$$\% \text{ loss} = \frac{\text{Initial wt. of tablets - Final wt. of tablets}}{\text{Initial wt. of tablets}} \times 100$$

WEIGHT VARIATION:
Twenty tablets were weighed individually and the average weight was determined. Then percentage deviation from the average weight was calculated. Deviation should not exceed the values given in table

Table.4: Standard Limit Value In Weight Variation Test

Average weight of a tablet	Percentage Deviation
80 mg or less	±10
>80 and <250mg	±7.5
250mg or more	±5

DRUG CONTENT (7)**:**
Ten tablets were weighed and powdered and 250 mg equivalent weight of clarithromycin was accurately weighed and transferred into a 100 ml volumetric flask. It was dissolved and made up the volume with 0.1N HCl pH 1.2. Subsequently the solution in volumetric flask was filtered and suitable dilutions were made and analyzed at 275 nm using UV-Visible spectrophotometer (Shimadzu UV-1601). The drug content of each sample was estimated from standard curve of clarithromycin using 0.1N HCl pH 1.2.

TABLET DENSITY (8)**:**
Tablet density is an important parameter of gastro retentive floating tablets as the tablets will float only when its density is less then that of gastric fluid (1.004). Densities of tablets were determined by using relation.

$$V = \pi r2\ h$$
$$D = m/v$$

Where, v = volume of tablet (cc), r = radius of tablet (cm), h = crown thickness of tablet (g/cc), m= mass of tablet.

BUOYANCY DETERMINATON (9)**:**
The time between introduction of dosage form and its buoyancy in the simulated gastric fluid i.e 0.1 N HCL and duration of buoyancy (total floating time) was measured. Tablet was introduced in beaker containing simulated gastric fluid. The time taken for dosage form to emerge on the surface of medium is buoyancy lag time and total duration of time by which dosage form remains buoyant is known as total floating time.

IN –VITRO **DISSOLUTION STUDIES** (10)**:**
The release rates of clarithromycin from tablets were determined using USP dissolution testing apparatus (paddle type). The test was performed using 900 ml of 0.1 N HCl at 37 ± 0.5°C and 50rpm for study. Aliquot volume of 5 ml was withdrawn at regular intervals. The samples were replaced with fresh dissolution medium. After filtration, the amount of drug release was determined from the standard calibration curve of pure drug.

RESULTS AND DISCUSSION

Micromeritic Properties:
ANGLE OF REPOSE:
The results of angle of repose were ranged between 24.19 ± 1.38 to 25.70 ± 0.70, which indicates good flow properties of powder.

CARR'S INDEX:
The Carr's index values were found to be in the range of 14.48 ± 0.005% to 16.35± 0.27%. These findings indicated that the powder mixture of all batches of formulation exhibited good flow properties.

Table.5: Evaluation Of Preformulation ParametersMicrometric of Clarithromycin gastro-retentive tablets

Formula code	Angle of repose	Bulk density	Tapped density	Carr's index
A	24.36±0.93	0.464±0.002	0.532±0.006	14.56±0.76
B	25.70±0.70	0.485±0.004	0.555±0.004	14.48±0.005
C	24.19±1.38	0.468±0.002	0.536±0.006	14.58±0.70
D	25.29±1.17	0.489±0.005	0.559±0.005	14.65±0.16
E	25.64±1.16	0.464±0.016	0.559±0.08	16.35±0.27
F	24.39±1.21	0.469±0.021	0.518±0.073	15.24±0.43

Evaluation of Physicochemical Parameters:

TABLET THICKNESS:

Thickness of the developed formulations A to F varied from 5.38± 0.02 mm to 5.56± 0.02 mm.

TABLET HARDNESS:

Hardness of the developed formulations A to F varied from 3.9± 0.10 kg/cm2 to 4.7± 0.05 kg/cm2.

FRIABILITY:

Friability of the developed formulations varied from 0.14 ± 0.18 % to 0.83± 0.36 % loss which was less than 1% as per official requirement of IP.

WEIGHT VARIATION:

The average weight of twenty tablets was calculated for each formulation which varied from 692.66 ± 16.80 mg to 705.66 ± 8.50 mg that complied the official requirement as per IP.

UNIFORMITY OF DRUG CONTENT:

The drug content varied from 95.41 ± 0.06 % to 105.15 ± 0.33 % which was within the required limits.

DIAMETER OF THE TABLET:

The diameter of the tablets varied from 12.62 ± 0.01 to 12.63 ± 0.02 mm

TABLE NO-6: Physicochemical parameters of developed gastro retentive tablets of Clarithromycin

Formula Code	Hardness	friability	Weight variation	diameter	Drug content	thickness
A	4.0±0.10	0.59±0.31	692.66±16.80	12.62±0.01	98.42±0.13	5.41± 0.02
B	3.9±0.10	0.68±0.26	700.66±18.77	12.63±0.02	95.41±0.06	5.38± 0.02
C	4.2±0.15	0.54±0.21	705.66±8.50	12.62±0.03	99.42±0.45	5.42± 0.02
D	4.1±0.25	0.14±0.18	697.66±3.21	12.63±0.02	98.01±0.21	5.51± 0.01
E	4.7±0.05	0.43±0.12	687.33±9.07	12.62±0.04	105.15±0.33	5.56± 0.02
F	4.5±0.15	0.83±0.36	700.33±15.94	12.62±0.03	103.78±0.18	5.45± 0.02

All values are mean of 3 readings ± standard deviation

BUOYANCY/ FLOATING TEST:

The tablet floating lag time (FLT) was found to be 80 sec to 115 sec and floating time more than 12 h. The floating time may be explained as a result of the time required for dissolution medium to penetrate the tablet matrix and develop the swollen layer for entrapment of CO^2 generated in-situ. The tablet mass decreases progressively due to liberation of CO^2 and release of drug from matrix. On the other side, as solvent front penetrated the glassy polymer layer, the swelling of HPMC K15M, HPMC K100M and Guar Gum caused an increase in volume of the tablet. The combined effect is a net reduction in density of the tablet which prolongs the duration of floatation beyond 12 h.

TABLET DENSITY:

The tablet density was found to be uniform among different batches of floating tablets and ranged from 0.87 to 0.98 g/cm3 The tablet density is less than gastric fluid both before and after ingestion so the tablets float on the surface of the gastric fluid for as long as 12 h.

Table.7:Results Of Tablet Density, Buoyancy Time And Total Floating Time

Formula code	Tablet density	Buoyancy lag time	Total floating time
A	0.90	34 sec	>12
B	0.87	25 sec	>12
C	0.95	54 sec	>12
D	0.92	42 sec	>12
E	0.98	87 sec	>12
F	0.97	71 sec	>12

***IN VITRO* DRUG RELEASE STUDIES:**

Floating tablets were prepared by using two viscosity grades of HPMC and Guar gum. In all the formulations it was observed that the release rate of drug was a function of HPMC K15M, HPMC K100M and Guar Gum content. From the *in vitro* dissolution data it was found that formulation F containing Guar Gum alone release 87.4% of drug

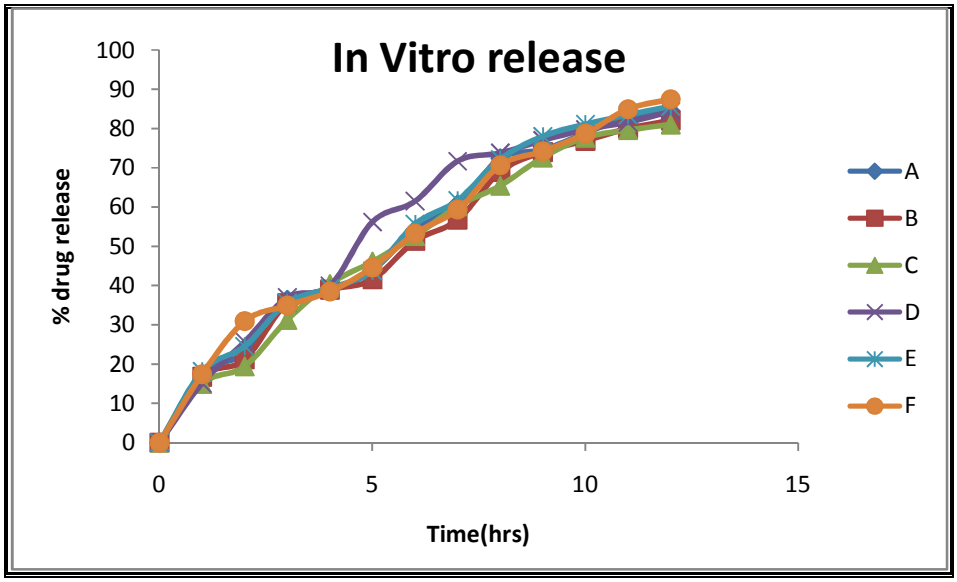
within 12 hours of study indicating that polymer is sufficient to control the drug release. Formulation C containing HPMC K4M and HPMC K15M showed better control of drug release than HPMC K4M alone, i.e. 81.06% at the end of 12 hours. Tablets of batches A and B containing combination of polymer showed release of 84.42% and 82.08%. Amongst all formulation studied controlled release was best observed in formulation containing HPMC K15M and HPMC K100M.

Table.8: *In Vitro* Drug Release Study

Time	A	B	C	D	E	F
1	17.46±0.44	16.74±0.90	14.94±0.90	15.12±1.71	18.12±0.54	17.36±0.58
2	22.92±0.59	21.18±0.63	19.44±0.72	25.68±1.53	24.54±1.90	30.93±0.66
3	36.36±0.97	35.58±1.05	31.26±1.08	36.96±2.27	35.58±1.15	34.90±1.10
4	38.58±0.44	38.94±1.27	40.44±1.80	39.90±1.74	39.30±0.99	38.50±0.70
5	43.92±0.58	41.58±0.64	46.14±1.92	56.22±7.35	43.74±0.90	44.60±0.90
6	54.18±1.02	51.36±1.53	52.62±1.55	61.50±6.91	55.62±2.88	53.26±0.94
7	60.72±0.44	56.76±2.02	60.24±1.71	71.70±1.57	61.68±0.92	59.36±1.45
8	72.42±1.52	68.94±1.29	65.46±2.74	73.80±2.38	72.14±0.52	70.63±0.90
9	74.64±1.19	74.04±1.84	72.66±2.16	76.98±3.06	78.00±1.55	74.23±0.90
10	78.84±0.14	76.86±1.53	77.72±1.18	79.74±3.12	81.06±0.72	78.70±0.55
11	82.98±0.38	80.04±0.74	79.62±0.92	81.60±2.70	83.46±0.72	84.93±0.94
12	84.42±0.38	82.08±0.82	81.06±1.55	84.30±1.17	85.62±0.45	87.46±0.94

Figures of % drug release are mean of triplicate study

Fig.4: Drug Release Pattern Of Different Batches Of Gastro Retentive Tablets Of Clarithromycin



CONCLUSION

It is evident from this study that gastro retentive tablet of an antibacterial drug clarithromycin can be formulated as an approach to increase gastric residence time and thereby improve its bioavailability. Formulation F containing Guar Gum prolonged the release (87.4% up to 12 hours) of the drug as compared to other prepared formulation. Thus the objective of formulating a floating dosage form of clarithromycin has been achieved.

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