Formulation and evaluation of mucoadhesive tablet of Clarithromycin

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ABSTRACT

The present investigation concerns the development of mucoadhesive tablets of Clarithromycin which were designed to prolong the gastric residence time after oral administration. Matrix tablets of Clarithromycin were formulated using four mucoadhesive polymers namely Carbopol 974P, HPMC K15M, HPMC K4M, HPMCK100M carried out studies for weight variation, thickness, hardness, content uniformity, swelling index, mucoadhesive force and in vitro drug release. Formulation of C9 and C12 which were formulated by using polymers, HPMC K14M, HPMC K15M, HPMCK100M and Carbopol 974P provided controlled release of Clarithromycin over the period of 12 hrs. The cumulative % of drug release of formulation C9 (98.71%) respectively.

Keywords: Mucoadhesive tablets, Clarithromycin, *in-vitro* release.

INTRODUCTION

A number of advancement has been made recently in the development of new technique for drug delivery, the technique capable of regulating the rate of drug delivery system. The conventional dosage forms stays in the stomach for 0.5-3 hours and passes to small intestines from where it gets absorbed within 3-6 hours. It is therefore difficult to adjust release retardation and stomach retention for longer period of time. Some antibiotics produce effect depending on concentration at the site of bacterial infection. The bioavailability of active ingredients which are not completely absorbed decreases because part of the dose is lost, so frequent administration of dosage form is required. Clarithromycin is used to treat certain infections caused by bacteria, such as pneumonia (a lung infection), bronchitis (infection of the tubes leading to the lungs), and infections of the ears, sinuses, skin, and throat. It also is used to treat and prevent disseminated Mycobacterium avium complex (MAC) infection. It is used in combination with other medications to eliminate H. pylori, a bacteria that causes ulcers. Clarithromycin is in a class of medications called macrolide antibiotics. It works by stopping the growth of bacteria. Antibiotics will not work for colds, flu, or other viral infections. Clarithromycin (CL) has a short half-life 2.5-3 hours. The usual oral dosage regimen is 250-500 mg every 4-6 hours and Gastric residence time of the conventional Clarithromycin dosage form is 0.5-2 hours. CL is having suitable properties stability in stomach pH and soluble in acidic pH. By considering above facts, the present study was undertaken with the following objective to design the controlled release mucoadhesive oral tablet to increase the residence time of the drug in the stomach and release for extended period of time in order to increase bioavailability of the drug, Reduce the dosing frequency, Improve patient compliance.

MATERIALS AND METHODS

Clarithromycin procured from Micro advance research centre,Banagalore, HPMC K4M, HPMC K15M, HPMC K100M purchased from Colorcon Asia pvt.Ltd, mumbai, Carbopol-974P purchased Noveon, Mumbai, India India; Mannitol, Mg-stearate purchased from Loba Chemie Pvt Ltd, Mumbai, India.

Formulation of muco adhesive tablets: Clarithromycin, HPMC K4M, HPMC K15M, HPMC K100M, Carbopol 974P and Mannitol were blended homogeneously in mortar as the quantity given in Table 3. Blended mixture was passed through the 60# Sieve and magnesium stearate 1% was added and blended. The homogeneously blended mixture was compressed in rotary tablet press with the 13.7 mm flat punch.

Table.1.Formulation of Mucoadhesive Clarithromycin tablets

Ingredients	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12
Clarithromycin	250	250	250	250	250	250	250	250	250	250	250	250
HPMCK4M	100	-	-	90	-	-	100			100		
HPMCK15M	-	100	-	-	90	-		100			100	
HPMC100M	-	-	100	-	-	90			100			100
Carbopol-974P	-	-	-	10	10	10	20	20	20	30	30	30
Magnesium stearate	5	5	5	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5	5	5	5
Mannitol	90	90	90	90	90	90	70	70	70	60	60	60

DSC study: DSC study shows that Clarithromycin gave sharp peak at the 220ºC.

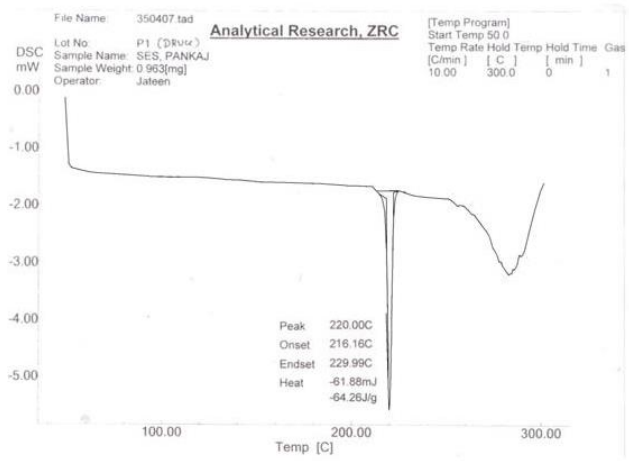


Figure.1.DSC Thermograph of Clarithromycin

EVAUATION OF MUCOADHESIVE TABLETS

Thickness: To determine uniformity of the diameter and thickness 20 tablets were selected and diameter as well as thickness was measured using vernier caliper. The average diameter and thickness of the tablet was calculated. The test was passed if none of the individual diameter and thickness value deviated by ±5% of the average

Hardness of Tablet: Monsanto hardness tester was used to check the hardness of the tablet. Tablet was placed vertically between the jaws of the tester. The two jaws placed under tension by a spring and screw gauge. By turning the screw, the load was increased, and at collapse the applied pressure from the spring was measured in kg. The test was done on six tablets.

Friability Test of Tablet: Tablets were subjected to tumbling in Roche friability tester. Six tablets were weighted and tumbled at the rate of 25rpm for 4min. The tablets were weighted and percent friability was calculated by the following formula.

$$\%F = (W_o - W) / W_o \times 100$$

Where F = friability

W_o = initial weight of the six tablets

W = final weight of the six tablets.

Tablets that loose less than 1% of weight are generally considered acceptable. The experiment was done in triplicate.

Weight Variation: Since the average weight of tablet is more than 250 mg, the test requirements are met if none of the individual weights are less than 95% or more than 105% of the average weight.

Uniformity of Weight: As per IP 1996 this test is applicable to the formulations containing less than 10 mg or less than 10% w/w of active ingredients. As the drug content is more than 10 % w/w, this test was not applicable.

Assay procedure of tablet: Twenty tablets were weighed and crushed to obtain a fine powder. An accurately weighted sample equivalent to 100 mg of CL was taken in

a stoppered volumetric flask (100 ml); 50ml of acidic buffer pH1.2 was added. The solution was filtered through whatmann filter paper (No 41) and the volume was made up to the mark with the same solvent. The aliquot portions of above solutions were further diluted with HCL buffer of 1.2 pH get final concentration of about 100 µg/ml CL and absorbance were measured at 485 nm against blank. The concentrations of drugs in sample were calculated.

Table.2.Physical properties of Clarithromycin tablets

Formulation No.	Hardness (kg/cm^2)	Thickness (cm)	% Friability	Weight Variation(mg)	% Drug content
C1	4.6±0.141	0.284±0.038	0.52	456±5.08	98.41
C 2	3.8±0.281	0.321±0.049	0.92	424±2.12	99.94
C 3	6.3±0.212	0.373±0.072	0.85	467±1.78	97.52
C 4	5.3±0.152	0.398±0.067	0.85	46115.87	96.94
C 5	4.1±0.141	0.281±0.0056	0.71	463±1.23	98.11
C6	5.2±0.282	0.363±0.089	0.89	452±2.11	99.52
C7	5.7±0.142	0.391±0.045	0.99	457±1.34	94.82
C8	8.8±0.703	0.323±0.011	0.94	459±1.31	97.05
C 9	5.3±0.624	0.367±0.016	0.90	460±1.22	93.41
C10	6.3±0.534	0.371±0.029	0.86	456±1.78	92.75
C11	6.2±0.312	0.354±0.023	0.81	452±1.82	95.65
C12	5.5±0.213	0.321±0.012	0.82	442±2.83	98.48

(n=6, ±S.D.)

Mucoadhesive Force Measurement of Tablet: Adhesion was reported to be effected by hydration. Hydration of the mucoadhesive polymer is essential to initiate the mucoadhesive bonding process. In case of tablets applied in the dehydrated state, which is most convenient, it is essential that sufficient water is available so that rapid hydration takes place, and a flexible rubbery state occurs. The capillary force arises when water from the space between the mucosa and the polymer was taken up by a dry system. Once the bond is formed, reduction in the rate of swelling due to water uptake from the tissue surface may only prolong the association of the tablet with the mucosa. Removal of water from the underlying mucosa layer by the hydrating polymer may increase the cohesive forces of mucus; this plays a vital role in the establishment of an effective mucoadhesive bond. Modified balance method was used for the measurement of mucoadhesive force. During measurement of mucoadhesive force 15 min contact time was kept constant.

Table.3.Mucoadhesive strength and force of formulation C 1 to C 12

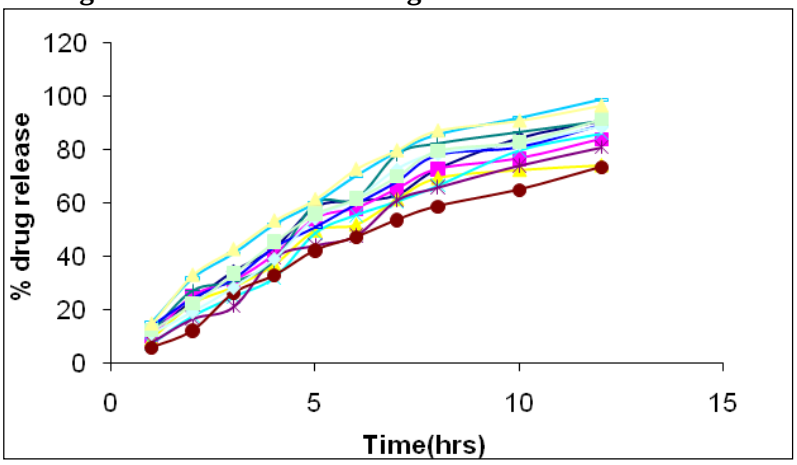
Formulation No	Mucoadhesive Strength (gm)	Mucoadhesion Force (dyne)
C 1	11.25±1.12	1.12
C 2	15.89±1.27	1.16
C3	16.93±2.37	1.85
C 4	29.89±1.92	2.14
C 5	23.78±1.46	2.32
C 6	32.27±1.36	3.16
C 7	21.69±1.23	3.20
C8	47.43±1.18	3.07
C 9	32.46±2.25	3.27
C 10	37.93±2.34	3.32
C11	32.37±2.49	4.25
C12	41.48±1.67	4.65

(n=6, ±S.D.)

***In-Vitro* Release Study of Mucoadhesive Tablet:** *In-vitro* release study of tablets was done by using USPXXII dissolution test apparatus. Jar was filled with HCl buffer pH 1.2 and temperature was maintained at 37±0.5 ^{0}C.

Paddle was revolved at 100 rpm speed. Five ml of sample was withdrew after interval of 1 hour and replaced with 5 ml of fresh dissolution medium to maintain sink condition. Samples were then analyzed spectrophotometrically for drug content at 485 nm. The release data obtained were fitted different equation to determine the corresponding release rate and mechanism of drug release from the floating-mucoadhesive tablet.

Figure.1.Cumulative % Drug Release Formula C1-C12



CONCLUSION

For the formulation of oral mucoadhesive tablet various polymer used like Hydroxy propyl methylcellulose K15M, Hydroxy propyl methylcellulose K4M, Carbopol 974P, used as hydrophilic matrix forming and mucoadhesive polymer in varying concentration along with Magnesium stearate, talc and Manitol as filler. A result of the study of individual polymers shows that the, HPMC K15M, HPMCK100M, HPMC K4M and Carbopl 974P, alone was also able to control the release in 12 hour. Release of Clarithromycin, from combination of HPMC K15M with Carbopl 974P, combination HPMC K4M with Carbopl 974P, combination HPMC K100M with Carbopl 974P gave the good results compared to employing individual polymers. Tablets of Batch F9 selected as an optimum batch.

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