RESEARCH ARTICLE

FORMULATION AND CHARACTERIZATION OF CLARITHROMYCIN FLOATING TABLETS BY USING VARIOUS POLYMERS

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Abstract
The present study outlines a systematic approach for designing and development of Clarithromycin floating tablets to enhance the bioavailability and therapeutic efficacy of the drug. Floating tablets of Clarithromycin have shown sustained release there by proper duration of action at a particular site and are designed to prolong the gastric residence time after oral administration. Different formulations were formulated by using direct compression technique. A floating drug delivery system (FDDS) was developed by using sodium bicarbonate as gas-forming agent and Chitosan, HPMC K4M and Ethyl cellulose as polymers. The preformulation parameters like Organoleptic properties, angle of repose, bulk density, tapped density, Hausner’s ratio, carr’s index and compressibility index of pure drug was evaluated and complied with the pharmacopoeial specifications. FTIR studies showed there was no interaction between drug and polymer. The prepared tablets were evaluated in terms of their physical characteristics, post compression parameters; in vitro release and buoyancy lag time the results of the in vitro release studies showed that the optimized formulation (C7) could sustain drug release for 12 hrs by using Ethyl cellulose in the concentration of 50 mg. The in vitro drug release followed Kors Mayer peppas release. Results revealed that the floating formulation of the Clarithromycin is the best formulation to obtain better therapeutic effect and Ethyl cellulose at a concentration of 50mg up to some extent it increases the Bioavailability of the drug to retain the dosage form on the desired site for effective period of the time.

Introduction:-
Gastric Floating Drug Delivery systems (GFDDS)
The various buoyant preparations include tablets, pills, granules, powders, capsules, hollow, Microspheres (micro balloons) and laminated films GFDDS1.

Non-Effervescent GFDDS2
The approach involved in the formulation of floating dosage forms is intimate mixing of drug with a gel forming hydrocolloid, which swells in contact with gastric fluid after oral administration and maintains a relative integrity of shape and a bulk density of less than one within the outer gelatinous barrier as shown in figure 1a.
Effervescent GFDDS:
The floating drug delivery systems utilize matrices prepared with swellable polymers such as methocel, polysaccharides, effervescent components like sodium bicarbonate, citric acid and tartaric acid or chambers containing a liquid that gasifies at body temperature. The optimal stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76:1 carbon dioxide is released, causing the beads to float in the stomach. The matrices are fabricated so that upon contact with gastric fluid, carbon dioxide is liberated by the acidity of gastric contents and is entrapped in the gellyfied hydrocolloid.

Figure 1: Mechanisms of a) Swelling system b) Non-Effervescent and c) Effervescent GFDDS.

Materials and Methods:-
Chemicals Used
Clarithromycin Procured From Maxwell Life Science, Mumbai (India). Chitosan, and HPMC K4M from Colorcon Asia Pvt Ltd (Goa, India), Ethyl cellulose and talc from Chemdyes Corporation (Ahmedabad, India), NaHCO₃ and Citric acid from Poona Chemicals Laboratories (Pune, India) and Magnesium stearate from S.D. Fine Chemicals, Mumbai, India.

Instruments Used
Analytical Balance (Shimadzu, Japan.), FTIR Spectrophotometer (Bruker FTIR Germany (Alpha T)), Dissolution Apparatus (Electro lab TDT-08L), UV Spectrophotometer (U.V 1700 Shimadzu, Japan.), X-Ray diffractometer (Bruker-AXS- DHR-2).

Analytical method development
Construction of Standard Graph of Clarithromycin in 0.1N HCL buffer by using the UV method
10mg Clarithromycin pure drug was dissolved in 10ml of methanol (stock solution 1) from stock solution 1ml of solution was taken and made up with 10ml of 0.1N HCL (100μg/ml). From here 1ml was taken and composed with 10 ml of 0.1N HCL (10μg/ml). The above solution was further diluted with 0.1N HCL to obtain a series of dilutions containing 2, 4, 6, 8, 10g/ml of per ml of solution. The absorbance of the above dilutions was measured at 210nm by using UV-Spectrophotometer taking 0.1N HCL as blank. Then plotted a graph of concentration on the X-Axis and Absorbance on Y-Axis which gives a straight line Linearity of standard curve is evaluated from the square of correlation coefficient (R²) which determined by least-square linear regression analysis.

Precompression Studies
Angle of repose
The angle of repose is calculated using the following formula:
\[ \tan \theta = \frac{h}{r} \]
\[ \theta = \text{Angle of repose} \]
\[ h = \text{Height of the cone}, \quad r = \text{Radius of the cone base} \]

Bulk density
The bulk density is calculated using the formula:
\[ \text{Bulk Density} = \frac{M}{V_o} \]
Where, \( M \) = weight of sample
\( V_o \) = apparent volume of sample

Tapped density
The exploited density is calculated, in gm per L, using the formula:
Tap = M / V
Where, Tap = Tapped Density
M = Weight of sample
V = Tapped volume of powder

**Measures of powder compressibility**

The Compressibility Index (Carr’s Index) is a measure of the tendency of a powdertobecompress.intheCompressibility Indexwhichiscalculated using the following formula:

Carr’s Index = [(tap - b) / tap] × 100
Where, b = Bulk Density
Tap = Tapped Density

**Formulation development of floating Tablets of Clarithromycin**

**Procedure for direct compression method:**
1. Drug and all other ingredients were individually passed through sieve 60.
2. All the ingredients were mixed thoroughly by triturating up to 15 min.
3. The powder mixture was lubricated with talc.
4. The tablets were prepared by using direct compression method by using 12 mm punch.

**Table 1:** Formulation composition for Floating tablets.

| INGREDIENTS | FORMULATION CODE |
|-------------|------------------|
| (MG)        | C1   | C2   | C3   | C4   | C5   | C6   | C7   | C8   | C9   |
| Clarithromycin | 250  | 250  | 250  | 250  | 250  | 250  | 250  | 250  | 250  |
| Chitosan     | 50   | 100  | 150  | -    | -    | -    | -    | -    | -    |
| HPMC K4M     | -    | -    | -    | 50   | 100  | 150  | -    | -    | -    |
| Ethyl cellulose| -   | -    | -    | -    | -    | -    | 50   | 100  | 150  |
| NaHCO₃       | 20   | 20   | 20   | 20   | 20   | 20   | 20   | 20   | 20   |
| Citric acid  | 15   | 15   | 15   | 15   | 15   | 15   | 15   | 15   | 15   |
| Magnesium stearate | 5   | 5    | 5    | 5    | 5    | 5    | 5    | 5    | 5    |
| Talc         | 4    | 4    | 4    | 4    | 4    | 4    | 4    | 4    | 4    |
| Lactose      | 156  | 106  | 56   | 156  | 106  | 56   | 156  | 106  | 56   |
| Total weight | 500  | 500  | 500  | 500  | 500  | 500  | 500  | 500  | 500  |

All the quantities were in mg

**Evaluation of post compression parameters for prepared Tablets**

The designed compression tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content.

**Average Weight**

The percent deviation is calculated using the following formula.

\[
\text{% Deviation} = \left( \frac{\text{Individual weight} - \text{Average weight}}{\text{Average weight}} \right) \times 100
\]

**Hardness**

Hardness of tablets was determined using Monsanto hardness tester and the average is calculated and presented with deviation.

**Thickness**

The mean thickness for core and coated tablets were calculated and presented with a deviation.

**Friability**

It is measured of mechanical strength of tablets. Roche friabilator was used to determine the friability by following procedure. Preweighed tablets were placed in the friabilator. The tablets were rotated at 25 rpm for 4 minutes (100 rotations). At the end of the test, the tablets were reweighed and the tablet weight loss was a measure of friability and is expressed as a percentage as

\[
\text{% Friability} = \left( \frac{W1 - W2}{W1} \right) \times 100
\]
Where, W₁ = Initial weight of tablets
W₂ = Weight of the tablets after test

**Determination of drug content**
Both squeeze-coated tablets were tested for drug content. Ten tablets were finely powdered quantities of the powder equivalent to one tablet weight of Clarithromycin were accurately weighed, transferred to a 100 ml volumetric flask containing 50 ml water and were allowed to stand to ensure complete solubility of the drug. The mixture was made up to volume with water. The solution was appropriately diluted and the absorbance was determined with a UV –Visible spectrophotometer. Drug concentration was calculated from the calibration curve.

**In vitro Buoyancy studies**
*In vitro* buoyancy is determined from the fluctuation time and the total fluctuation time. (As per the method described by Rosa et al) The tablets were placed in a 100ml beaker containing 0.1N HCL. The time required for the tablet to rise to the surface and float was determined as floating lag time (FLT) and the length of time the tablet fluctuated continuously based on the melting medium was recorded as Total Floating Time.

**In vitro drug release studies**
**Procedure**
900ml of 0.1 HCL was placed on board and USP II equipment (Paddle Method) assembled. The medium was allowed to equilibrate to temp of 37°C ± 0.5°C. Tablet was placed in the vessel and the vessel was covered the apparatus was operated for 12 hours and then the medium 0.1 N HCL was taken and process was continued from 0.5 to 12hrs at 50 rpm. At the specified time interval 5ml of the receptors fluid is withdrawn, filtered and back 5ml of receptor fluid is replaced. Suitable dilutions were done with media and analyzed by spectrophotometrically at 210nm using UV-spectrophotometer.

**Application of release rate kinetics to dissolution data**
Various models have been tested to explain drug release kinetics. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

**Fourier Transform Infrared (FTIR) studies**
Compatibility between pure drug and excipient was detected by the FTIR spectrum obtained on the german Bruker FTIR (Alpha T). The solid powder sample is placed directly on the yellow crystal that is made up of ZnSe. The spectra were recorded over the wave number of 4000cm⁻¹ to 550cm⁻¹.

**Powder X-ray diffraction**
X-Ray diffraction pattern of pure drug, and Polymers were examined by using X-Ray diffractometer (Bruker-AXS-DHR-2) using Cr filtered (a) radiations, a voltage of 40kv, current of 25mA and receiving slit of 0.2 In. The instruments were operated over 2? Scale. The angular range was 5 to 50o(2?) and counts were accumulated for 0.8 second at each step.

**Results and Discussion:-**
**Preparation of Calibration curve for Clarithromycin**
**Table 2:** Calibration curve of Clarithromycin.

| Conc [µg/mL] | Abs   |
|--------------|-------|
|              | 0     |
| 2            | 0.137 |
| 4            | 0.261 |
| 6            | 0.378 |
| 8            | 0.497 |
| 10           | 0.613 |
The standard graph of Clarithromycin showed good linearity with $R^2$ of 0.999, which indicates that it obeys “Beer-Lamberts” law.

**Preformulation parameters of powder blend**

**Table 3:** Pre-Formulation Parameters of Blend.

| Formulation Code | Angle of Repose (°) | Bulk density (gm/mL) | Tapped density (gm/mL) | Carr’s index (%) | Hausner’s Ratio |
|------------------|---------------------|----------------------|------------------------|------------------|------------------|
| F1               | 22.44±0.2           | 0.58±0.01            | 0.66±0.01              | 11.8±2.2         | 1.13±0.02        |
| F2               | 22.83±0.4           | 0.43±0.03            | 0.50±0.02              | 13.2±2.0         | 1.15±0.02        |
| F3               | 23.31±0.3           | 0.47±0.02            | 0.55±0.03              | 14.2±2.0         | 1.16±0.23        |
| F4               | 23.44±0.4           | 0.50±0.01            | 0.58±0.01              | 14.9±2.2         | 1.17±0.03        |
| F5               | 22.16±0.2           | 0.48±0.02            | 0.55±0.01              | 12.1±4.9         | 0.65±0.23        |
| F6               | 23.37±0.4           | 0.53±0.03            | 0.58±0.04              | 8.6±2.2          | 1.09±0.03        |
| F7               | 23.53±0.5           | 0.55±0.02            | 0.61±0.03              | 9.8±2.0          | 1.11±0.03        |
| F8               | 23.77±0.4           | 0.55±0.01            | 0.59±0.02              | 6.7±2.0          | 1.07±0.03        |
| F9               | 23.04±0.3           | 0.54±0.01            | 0.57±0.01              | 5.26±2.0         | 1.06±0.02        |

The tablet powder mixture was subjected to various pre-formulation parameters. The residual angle value indicates that the powder mixture has good flow property. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.43±0.03 to 0.58±0.01 (gm/ml) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.50±0.02 to 0.66±0.01 showing the powder has good flow properties. The compressibility index of all the formulations was found to be below 14.96 which show that the powder has good flow properties. All the formulations has shown the hausners ratio ranging between 0.65 to 1.17 indicating the powder has good flow properties.

**Quality Control Parameters For tablets**

Table quality control tests such as weight variation, hardness, and friability, thickness, Drug content and drug release studies were performed for floating tablets.

**Table 4:** In vitro quality control parameters.

| Formulation codes | Average Weight (mg) | Hardness (kg/cm²) | Friability (%loss) | Thickness (mm) | Drug content (%) | Floating lag time(Sec) | Total floating time(Hrs) |
|-------------------|---------------------|-------------------|-------------------|----------------|-----------------|------------------------|--------------------------|
| F1                | 498.31              | 5.2               | 0.51              | 5.98           | 98.12           | 61                     | 10                       |
F2  497.68  5.9  0.46  5.31  96.35  50  11  
F3  499.20  5.1  0.35  5.29  99.80  38  12  
F4  498.18  5.0  0.72  5.73  98.14  42  9    
F5  500.03  5.9  0.69  5.18  98.58  31  10   
F6  499.10  6.3  0.31  5.27  97.21  25  12   
F7  498.71  5.2  0.53  5.90  99.30  20  12   
F8  496.38  5.7  0.42  5.14  98.14  31  12   
F9  498.64  6.1  0.38  5.65  98.05  35  12   

**Figure 2:** Floating lag time (Sec).

**Figure 3:** Total floating time (Hrs).

All the parameters such as weight variation, friability, hardness, thickness, drug content were found to be within limits.

**Buoyancy and total Flotation test**

From the results, it was observed that as the buoyancy lag time and the total floating time was studied for all the formulations, F1 to F9 total floating time were found to be respectively as shown in Table. The formulations with Chitosan polymer (F1, F2 and F3) showed high buoyancy lag time when compared to formulations with HPMC K4M polymer (F4, F5 and F6). For all the F5, F6, F7, F8 and F9 formulations showed more total floating time when compared to F1, F2, and F4. Results revealed that as the concentration of the Chitosan and HPMC K4M polymer increases, the buoyancy lagging time decreases. The increase in the concentration of the Ethyl cellulose polymer resulted in the increase of the buoyancy lag time.
In vitro drug release studies

Table 5: Dissolution data of floating tablets.

| TIME (HR) | F1    | F2    | F3    | F4    | F5    | F6    | F7    | F8    | F9    |
|-----------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| 0         | 0     | 0     | 0     | 0     | 0     | 0     | 0     | 0     | 0     |
| 1         | 18.92 | 14.29 | 11.65 | 20.82 | 13.12 | 10.05 | 18.78 | 13.96 | 08.42 |
| 2         | 26.56 | 19.10 | 16.35 | 26.91 | 19.30 | 18.96 | 29.98 | 18.81 | 15.39 |
| 3         | 31.80 | 24.09 | 20.12 | 35.36 | 28.28 | 23.19 | 37.31 | 24.75 | 21.58 |
| 4         | 37.12 | 28.68 | 26.49 | 42.52 | 36.17 | 29.53 | 45.94 | 30.29 | 28.34 |
| 5         | 42.27 | 35.75 | 31.26 | 58.81 | 43.52 | 36.31 | 50.42 | 36.81 | 43.23 |
| 6         | 48.93 | 42.81 | 37.16 | 65.99 | 58.78 | 41.79 | 56.79 | 45.34 | 48.06 |
| 7         | 55.10 | 49.59 | 42.90 | 75.28 | 63.80 | 46.52 | 61.28 | 50.78 | 56.14 |
| 8         | 60.47 | 56.15 | 48.21 | 77.29 | 78.43 | 53.47 | 68.41 | 56.99 | 60.27 |
| 9         | 67.34 | 62.79 | 51.86 | 79.80 | 87.47 | 59.59 | 75.60 | 62.15 | 67.39 |
| 10        | 72.81 | 67.99 | 56.06 | 83.23 | 89.59 | 66.76 | 80.15 | 67.72 | 72.95 |
| 11        | 86.85 | 72.38 | 65.16 | 86.75 | 91.08 | 80.11 | 91.72 | 83.63 | 78.38 |
| 12        | 96.59 | 89.42 | 79.73 | 98.43 | 97.14 | 86.49 | 99.70 | 90.82 | 85.12 |

**Fig: 4:** Dissolution data of Clarithromycin Floating tablets containing all formulations (Chitosan(F1-F3), HPMC K4M(F4-F6) and Ethyl cellulose(F7-F9)).

The cumulative percent of drug release from various formulations and release coefficients values of the various models for respective formulation were represented in tables 8.4 respectively.

Formulation F7 showed good drug release and buoyancy time than all other formulations.

The formulation F7 showed a constant release in a controlled manner with 99.70%. Hence F7 was chosen for kinetics studies.
Application of Release Rate Kinetics to Dissolution Data for optimised formulation

Table 6: Application kinetics for optimised formulation.

| CUMULATIVE (%) RELEASE Q | TIME (T) | ROG (%) RELEASE | LOG (T) | LOG (%) REMAIN | RELEASE RATE (CUMULATIVE % RELEASE /T) | 1/CUMULATIVE % RELEASE | PEP (% Drug Remaining) | Q0 1/3 | Qt 1/3 | Q0 1/3 - Qt 1/3 |
|--------------------------|---------|----------------|---------|----------------|---------------------------------------|------------------------|------------------------|--------|--------|------------------|
| 0                        | 0       | 0              | 2.000   | 0              | 100                                   | 4.62                   | 4.64                   | 0.00   | 0.00   |                  |
| 18.78                    | 1       | 1.00           | 1.274   | 0.00           | 18.780                                | 4.62                   | 4.33                   | 0.31   | 11     |                  |
| 29.98                    | 2       | 1.40           | 1.477   | 0.301          | 14.990                                | 4.62                   | 4.12                   | 0.51   | 20     |                  |
| 37.31                    | 3       | 1.73           | 1.572   | 0.477          | 12.437                                | 4.62                   | 3.97                   | 0.69   | 69     |                  |
| 45.94                    | 4       | 2.00           | 1.662   | 0.602          | 11.485                                | 4.62                   | 3.78                   | 0.86   | 60     |                  |
| 50.42                    | 5       | 2.23           | 1.703   | 0.699          | 10.084                                | 4.62                   | 3.67                   | 0.99   | 68     |                  |
| 56.79                    | 6       | 2.49           | 1.754   | 0.778          | 9.465                                 | 4.62                   | 3.50                   | 1.10   | 32     |                  |
| 61.28                    | 7       | 2.64           | 1.787   | 0.845          | 8.754                                 | 4.62                   | 3.38                   | 1.20   | 59     |                  |
| 68.41                    | 8       | 2.82           | 1.835   | 0.903          | 8.551                                 | 4.62                   | 3.16                   | 1.40   | 80     |                  |
| 75.6                     | 9       | 3.00           | 1.879   | 0.954          | 8.400                                 | 4.62                   | 2.90                   | 1.70   | 41     |                  |
| 80.15                    | 10      | 3.12           | 1.904   | 1.000          | 8.015                                 | 4.62                   | 2.70                   | 1.90   | 34     |                  |
| 91.72                    | 11      | 3.31           | 1.962   | 1.041          | 8.338                                 | 4.62                   | 2.02                   | 2.61   | 19     |                  |
| 99.7                     | 12      | 3.46           | 1.999   | 1.079          | 8.308                                 | 4.62                   | 0.66                   | 3.97   | 72     |                  |
Optimised formulation F7 was kept for release kinetic studies. From the above graphs it was evident that the formulation F7 was followed Korsmayer Peppas release mechanism.

**Drug – Excipient compatibility studies**

**Fourier Transform-Infrared Spectroscopy**

![FTIR Spectrum of pure drug](image)
There was no disappearance of any characteristics peak in the FTIR spectrum of drug and the polymers used. This shows that there is no chemical interaction between the drug and the polymers used. The presence of peaks at the expected range confirms that the materials taken for the study are genuine and there were no possible interactions.

Clarithromycin are also present in the physical mixture, which indicates that there is no interaction between drug and the polymers, which confirms the stability of the drug.

**XRD Studies**

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**Fig 10:** FTIR Spectrum of optimised formulation.

**Fig 11:** The X-ray diffraction analysis of pure drug.

**Fig 12:** The X-ray diffraction analysis of formulation.

Red colour: Pure drug, Blue:Chitosan, Pink:HPMC K4M, Green:Ethyl cellulose
Conclusion:
The preformulation parameters like angle of repose, bulk density, tapped density, Hausner’s ratio; Carr’s index of pure drug was evaluated and complied with the pharmacopoeial specifications. The analysis of XRD study shows that clarithromycin (pure drug) and polymer existed in crystalline in nature. FTIR study shows that there is no pharmaco-polymer interaction. Gastro retentive floating matrix tablets of Clarithromycin were successfully prepared with various polymers like Chitosan, HPMC K4M and Ethyl cellulose. The formulated batch was evaluated for physico-chemical parameters, floating properties and dissolution profile. From the evaluation results, it was observed that the tablets contain the higher viscosity Ethyl cellulose showed long floating lag time when compared to tablets prepared with other polymers. The physical properties such as hardness, weight change and friability most of the batches met the pharmacopoeial specifications. The drug content of all tablets is in the range of 96.35 – 99.80%. In vitro dissolution studies of all the formulations were carried out in 0.1 N HCL. The tablets containing Ethyl cellulose (F7) showed satisfactory results with short floating lag time (20 sec) total buoyancy time more than 12 h, cumulative % drug release (99.70%) and controlled drug release up to 12 h. So F7 was taken for kinetic studies. The kinetic studies were carried for formulation F7 showed high regression value of 0.992 for Korsmayer pepras release mechanism. Hence it was concluded that formulation C7 chosen as optimum formulation.

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