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FORMULATION AND EVALUATION OF AZITHROMYCIN SUSTAIN RELEASE TABLETS

Alige Sudharani*, T. Vijaya kumari, Dr. D. Venkata ramana.
Department of Pharmaceutics,Holy Mary Institute of Technology and Science (College of Pharmacy),Keesara - Bogaram - Ghatkesar, Telangana 501301.

Abstract:
Today's goal was to transfer two (200 mg) of a two-way direct compression matrix into two durable free matrix bearings, using polymers like chewing gum, pectin and. Two studies on the two drugs were carried out two combinations. Two studies were conducted on both tablets, drug release, two kinetic researches. The FTIR confirmed that two of them had become two without the interaction between polymers and drugs. The pony houses were placed at the edges. Both should be better used to manage or maintain infections that have been demonstrated or suspected of being cut by microorganisms if they choose to develop antimicrobial resistance and develop the efficacy of two seeds of two forms optimized for a duration of 12 hours. The kinetic treatment of the selected components (F8) found that the release of the drug follows the release kinetics. The results of the present seem to indicate the suitability of polymers for the practice of an extended-release device, in particular based on the matrix.

Keywords: *Azithromycin, Acacia, Pectin and Karaya gum and Sustained release tablets.*

Corresponding author:
Alige Sudharani*
Department of Pharmaceutics,
Holy Mary Institute of Technology and Science (College of Pharmacy),
Keesara - Bogaram - Ghatkesar, Telangana.
Email Id- sudharuth18@gmail.com

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1. INTRODUCTION[1-9]:

Sustained release tablets are commonly taken only once or twice daily, compared with counterpart conventional forms that may have to take three or four times daily to achieve the same therapeutic effect. The advantage of administering a single dose of a drug that is released over an extended period of time to maintain a near-constant or uniform blood level of a drug often translates into better patient compliance, as well as enhanced clinical efficacy of the drug for its intended use.

The first sustained release tablets were made by Howard Press in New Jersy in the early 1950's. The first tablets released under his process patent were called 'Nitroglyn' and made under license by Key Corp. in Florida.

Sustained release, prolonged release, modified release, extended release or depot formulations are terms used to identify drug delivery systems that are designed to achieve or extend therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose.

The goal in designing sustained or sustained delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery. So, sustained release dosage form is a dosage form that release one or more drugs continuously in predetermined pattern for a fixed period of time, either systemically or to a specified target organ.

Sustained release dosage forms provide a better control of plasma drug levels, less dosage frequency, less side effect, increased efficacy and constant delivery. There are certain considerations for the preparation of extended release formulations:

- ✓ If the active compound has a long half-life, it is sustained on its own,
- ✓ If the pharmacological activity of the active is not directly related to its blood levels,
- ✓ If the absorption of the drug involves an active transport and
- ✓ If the active compound has very short half-life then it would require a large amount of drug to maintain a prolonged effective dose.

The above factors need serious review prior to design.

Introduction of matrix tablet as sustained release (SR) has given a new breakthrough for novel drug delivery system in the field of Pharmaceutical technology. It excludes complex production procedures such as coating and Pelletization during manufacturing and drug release rate from the dosage form is controlled mainly by the type and proportion of polymer used in the preparations. Hydrophilic polymer matrix is widely used for formulating an SR dosage form. Because of increased complication and expense involved in marketing of new drug entities, has focused greater attention on development of sustained release or controlled release drug delivery systems. Matrix systems are widely used for the purpose of sustained release. It is the release system which prolongs and controls the release of the drug that is dissolved or dispersed.

In fact, a matrix is defined as a well-mixed composite of one or more drugs with gelling agent i.e. hydrophilic polymers. By the sustained release method therapeutically effective concentration can be achieved in the systemic circulation over an extended period of time, thus achieving better compliance of patients. Numerous SR oral dosage forms such as membrane controlled system, matrices with water soluble/insoluble polymers or waxes and osmotic systems have been developed, intense research has recently focused on the designation of SR systems for poorly water soluble drugs.

1.1. RATIONALE FOR EXTENDED RELEASE DOSAGE FORMS[10-12]:

Some drugs are inherently long lasting and require only once-a-day oral dosing to sustain adequate drug blood levels and the desired therapeutic effect. These drugs are formulated in the conventional manner in immediate release dosage forms. However, many other drugs are not inherently long lasting and require multiple daily dosing to achieve the desired therapeutic results. Multiple daily dosing is inconvenient for the patient and can result in missed doses, made up doses, and noncompliance with the regimen. When conventional immediate-release dosage forms are taken on schedule and more than once daily, they cause sequential therapeutic blood level peaks and valleys (troughs) associated with the taking of each dose . However, when doses are not administered on schedule, the resulting peaks and valleys reflect less than optimum drug therapy. For example, if doses are administered too frequently, minimum toxic concentrations of drug may be reached, with toxic side effects resulting. If doses are missed, periods of sub therapeutic drug blood levels or those below the minimum effective concentration may result, with no benefit to the patient. Extended-release tablets and capsules are commonly taken only once or twice daily, compared with counterpart conventional forms that may have to be taken three or four times daily to achieve the same therapeutic effect. Typically, extended-release products provide an immediate release of drug that promptly produces the desired therapeutic effect, followed by gradual release of additional amounts of drug to maintain this effect over a predetermined period (Fig.1).

The sustained plasma drug levels provided by extended-release products oftentimes eliminate the need for night dosing, which benefits not only the patient but the caregiver as well.

1.2. Drawbacks of Conventional Dosage Forms[13]:

1. Poor patient compliance, increased chances of missing the dose of a drug with short half-life for which frequent administration is necessary.

2. A typical peak-valley plasma concentration time profile is obtained which makes attainment of steady-state condition difficult.
3. The fluctuations in drug levels may lead to precipitation of adverse effects especially of a drug with small Therapeutic Index (TI) whenever over medication occur.

1.3. TERMINOLOGY[14,15]:

Modified release delivery systems may be divided conveniently in to four categories.

A) Delayed release
B) Sustained release
- ✓ Controlled release
- ✓ Extended release

C) Site specific targeting
D) Receptor targeting

A) Delayed Release:

These systems are those that use repetitive, intermittent dosing of a drug from one or more immediate release units incorporated into a single dosage form. Examples of delayed release systems include repeat action tablets and capsules and enteric-coated tablets where timed release is achieved by a barrier coating.

B) Sustained release:

During the last two decades there has been remarkable increase in interest in sustained release drug delivery system. This has been due to various factor viz. the prohibitive cost of developing new drug entities, expiration of existing international patents, discovery of new polymeric materials suitable for prolonging the drug release, and the improvement in therapeutic efficiency and safety achieved by these delivery systems. Now-a-days the technology of sustained release is also being applied to veterinary products. These systems also provide a slow release of drug over an extended period of time and also can provide some control, whether this be of a temporal or spatial nature, or both, of drug release in the body, or in other words, the system is successful at maintaining constant drug levels in the target tissue or cells.

1. Controlled Release:

These systems include any drug delivery system that achieves slow release of drug over an extended period of time.

2. Extended Release:

Pharmaceutical dosage forms that release the drug slower than normal manner at predetermined rate & necessarily reduce the dosage frequency by two folds.

C) Site specific targeting:

These systems refer to targeting of a drug directly to a certain biological location. In this case the target is adjacent to or in the diseased organ or tissue.

D) Receptor targeting:

These systems refer to targeting of a drug directly to a certain biological location. In this case the target is the particular receptor for a drug within an organ or tissue. Site specific targeting and receptor targeting systems satisfy the spatial aspect of drug delivery and are also considered to be sustained drug delivery systems.

METHODOLOGY:

7.1. Analytical method development:

a) Determination of absorption maxima:

10mg of Azithromycin pure drug was dissolved in 10ml of Methanol (stock solution). 1ml of above solution was taken and make up with10ml by using 0.1 N HCl (100µg/ml).From this 1ml was taken and make up with 10 ml of 0.1 N HCl (10µg/ml) and similar procedure was done using pH 6.8 Phosphate buffer. UV spectrums was taken using Double beam UV/VIS spectrophotometer. The solution was scanned in the range of 200 – 400 nm.

b) Preparation calibration curve:

10mg of Azithromycin pure drug was dissolved in 10ml of Methanol (stock solution). 1ml of above solution was taken and make up with10ml by using 0.1 N HCl (100µg/ml).From this 1ml was taken and make up with 10 ml of 0.1 N HCl (10µg/ml). The above solution was subsequently diluted with 0.1N HCl to obtain series of dilutions Containing 5,10,15,20 and 25 µg/ml of Azithromycin per ml of solution. The absorbance of the above dilutions was measured at respective wavelength by using UV-Spectrophotometer taking 0.1N HCl as blank. Then a graph was plotted by taking Concentration on X-Axis and Absorbance on Y-Axis which gives a straight line Linearity of standard curve was assessed from the square of correlation coefficient (R^2) which determined by least-square linear regression analysis. The above procedure was repeated by using pH 6.8 phosphate buffer.

7.2. Drug – Excipient compatibility studies

Fourier Transform Infrared (FTIR) spectroscopy:

The formulations were subjected to FT IR studies to find out the possible interaction between the drug and the excipients during the time of preparation. FT IR analysis of the Pure drug and optimised formulation were carried out using an FT IR spectrophotometer (Agilent).

7.3. Formulation development of Tablets:

All the formulations were prepared by direct compression. The compositions of different formulations are given in Table. The tablets were prepared as per the procedure given below and aim is to prolong the release of Azithromycin. Total weight is 200mg.

Procedure:

1) Azithromycin and all other ingredients were individually passed through sieve no ≠ 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.

Table 7.3: Formulation composition for tablets

INGREDIENTS	FORMULATION CHART											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Azithromycin	25	25	25	25	25	25	25	25	25	25	25	25
Acacia	30	60	90	120	-	-	-	-	-	-	-	-
Pectin	-	-	-	-	30	60	90	120	-	-	-	-
Karaya gum	-	-	-	-	-	-	-	-	30	60	90	120
Lactose	134	104	74	44	134	104	74	44	134	104	74	44
Magnesium Stearate	6	6	6	6	6	6	6	6	6	6	6	6
Talc	5	5	5	5	5	5	5	5	5	5	5	5
Total Weight	200	200	200	200	200	200	200	200	200	200	200	200

RESULTS AND DISCUSSION:

The present study was aimed to developing Sustained release tablets of Azithromycin using natural polymers. All the formulations were evaluated for physicochemical properties and *in-vitro* drug release studies.

Analytical Method

Graphs of Azithromycin were taken in 0.1N HCl and in pH 6.8 phosphate buffer at 210 nm and 213nm respectively.

Standard graph in 0.1 N HCl (λ_{max} 210nm)

Standard graph of Azithromycin was plotted as per the procedure in experimental method and its linearity is shown in Table 8.1 and Fig 8.1. The standard graph of Azithromycin showed good linearity with R^2 of 0.998, which indicates that it obeys "Beer- Lamberts" law.

Table 8.1: Standard graph values of Azithromycin in 0.1 N HCl

Conc [µg/mL]	Absorbance
0	0
5	0.162
10	0.215
15	0.339
20	0.485
25	0.592

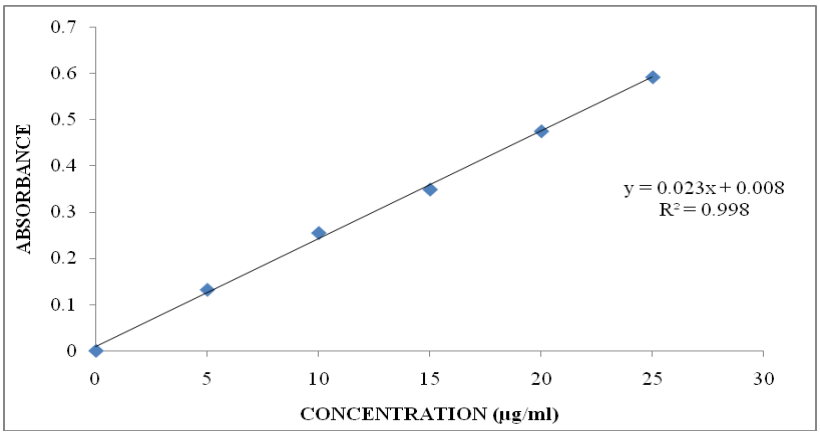


Fig 8.2: Standard graph of Azithromycin in 0.1 N HCl

Standard graph in phosphate buffer pH 6.8 (λ_{max} 213 nm)

Table 8.2: Standard graph values of Azithromycin in pH 6.8 phosphate buffer

Concentration (µg/mL)	Absorbance
0	0
5	0.158
10	0.248
15	0.361
20	0.481
25	0.591

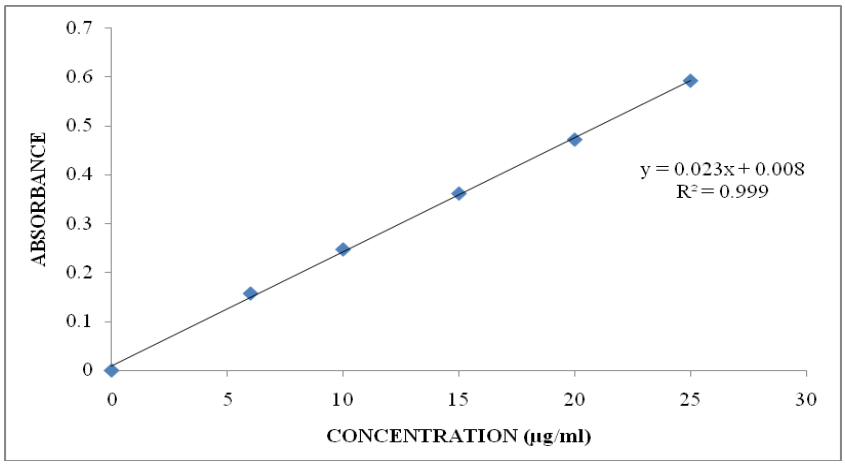
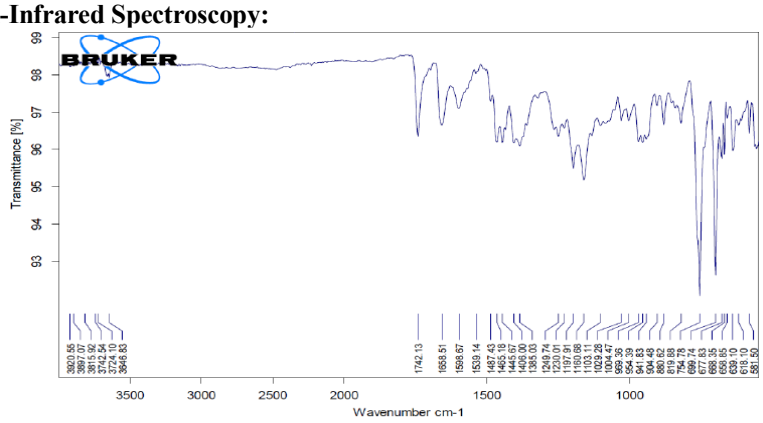


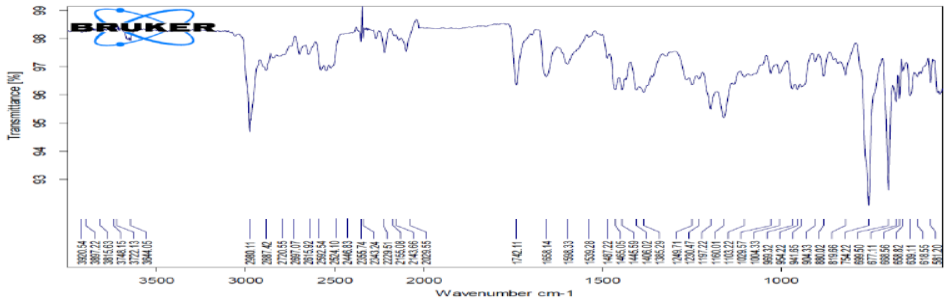
Fig 8.3 : Standard graph of Azithromycin in pH 6.8 phosphate buffer

Drug – Excipient compatability studies

Fourier Transform-Infrared Spectroscopy:



FT-TR Spectrum of Azithromycin pure drug.



FT-IR Spectrum of Optimised Formulation

From the above graphs it was showed no interactions between drug and excipients. Both API and excipients compatibility with each other.

Preformulation parameters of powder blend

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
F1	29.83±0.02	0.409±0.04	0.518±0.06	13.32±0.02	1.15±0.03
F2	30.96±0.06	0.405±0.05	0.468±0.06	13.46±0.01	1.15±0.04
F3	32.01±0.04	0.409±0.04	0.488±0.08	14.43±0.02	1.16±0.02
F4	28.01± 0.04	0.469±0.04	0.525±0.08	10.66±0.02	1.11±0.03
F5	26.32 0.06	0.45±0.08	0.548±0.02	18.88±0.03	1.21±0.02
F6	28.08±0.02	0.481±0.04	0.569±0.02	18.22±0.02	1.20±0.04
F8	25.18±0.03	0.459±0.02	0.58±0.02	19.48±0.02	1.24±0.01
F8	29.98±0.01	0.458±0.01	0.54±0.011	15.18±0.02	1.18±0.03
F9	23.85 ±0.01	0.446±0.05	0.539±0.09	18.25±0.08	1.20±0.02
F10	28.1±0.03	0.461±0.08	0.539±0.09	14.48±0.01	1.16±0.04
F11	26.58±0.05	0.405±0.06	0.5±0.04	19±0.02	1.23±0.03
F12	28.08±0.02	0.418±0.01	0.505±0.02	18.22±0.08	1.20±0.01

Pre-formulation parameters of Core blend

Tablet powder blend was subjected to various pre-formulation parameters. 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 0.405±0.0 6 to 0.481±0.04 (gm/cm3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.5±0.04 to 0.539±0.09 showing the powder has good flow properties. The compressibility index of all the formulations was found to be below 18 which show that the powder has good flow properties. All the formulations has shown the hausner ratio ranging between 0 to 1.25 indicating the powder has good flow properties.

Quality Control Parameters For tablets:

Tablet quality control tests such as weight variation, hardness, and friability, thickness, and drug release studies in different media were performed on the compression coated tablet.

***In vitro* quality control parameters for tablets**

Formulation codes	Weight variation(mg)	Hardness(kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)
F1	198.25	6.1	0.25	3.15	98.36
F2	198.24	6.5	0.61	3.21	98.51
F3	199.28	6.3	0.34	3.62	99.22
F4	198.31	6.8	0.18	3.41	98.15
F5	198.65	6.1	0.54	3.53	96.42
F6	199.82	6.9	0.31	3.19	98.14
F8	198.48	6.4	0.29	3.62	99.32
F8	195.33	6.5	0.36	3.18	96.48
F9	196.21	6.8	0.53	3.54	99.51
F10	198.82	6.3	0.49	3.12	98.15
F11	199.22	6.0	0.54	3.59	99.11
F12	200.01	6.6	0.62	3.42	98.52

Weight variation test:

Tablets of each batch were subjected to weight variation test, difference in weight and percent deviation was calculated for each tablet. The average weight of the tablet is approximately in range of 195.02±0.88 to 204.48±2.28 mg, The results of the test showed that, the tablet weights were within the pharmacopoeia limit.

Hardness test:

Hardness of the three tablets of each batch was checked by using Monsanto hardness tester. The results showed that the hardness of the tablets is in range of 6.0 to 6.9kg/cm^2, which was within IP limits.

Thickness:

Thickness of three tablets of each batch was checked by using micrometer and data shown .The result showed that thickness of the tablet is raging from 3.12 to 3.62mm.

Friability:
Tablets of each batch were evaluated for percentage friability and. The average friability of all the formulations lies in the range of 0.25 to 0.62which was less than 1% as per official requirement of IP indicating a good mechanical resistance of tablets. All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits.

***In Vitro* Drug Release Studies**

Table 8.5Dissolution Data of Azithromycin Tablets Prepared with Acacia

TIME (hr)	CUMULATIVE PERCENT DRUG DISSOLVED			
	F1	F2	F3	F4
0	0	0	0	0
0.5	18.88	12.23	15.41	11.58
1	26.89	19.93	20.59	16.94
2	35.84	23.24	26.93	20.62
3	49.92	30.85	31.83	24.86
4	56.41	34.51	38.51	32.35
5	62.82	38.10	42.32	38.45
6	68.28	41.16	46.89	44.80
8	83.48	55.82	65.24	48.25
8	80.68	60.88	68.10	55.24
9	86.12	68.14	82.85	59.83
10	91.85	83.48	86.98	62.34
11	95.28	89.95	81.18	68.52
12	98.16	89.62	86.42	83.48

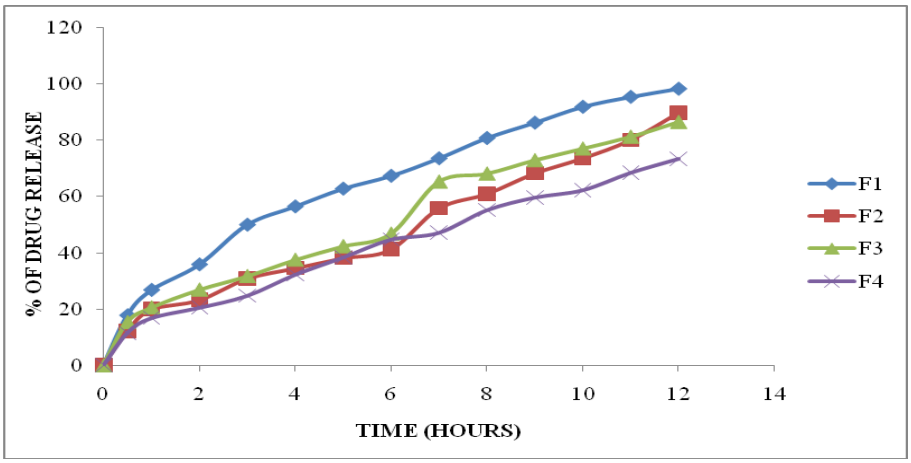


Fig 8.3Dissolution profile of Azithromycin (F1 –F4 formulations).

Table 8.6: Dissolution Data of Azithromycin Tablets Prepared With Pectin

TIME (hr)	CUMULATIVE PERCENT DRUG DISSOLVED			
	F5	F6	F8	F8
0	0	0	0	0
0.5	8.28	11.31	15.32	18.92
1	10.91	15.96	19.99	22.19
2	18.69	20.81	28.41	29.94
3	25.13	25.93	38.26	38.09
4	30.89	31.86	40.98	48.36
5	38.56	38.98	45.18	52.65
6	42.28	42.81	52.84	60.91
8	49.4	49.88	58.84	69.15
8	54.82	53.99	65.36	86.58
9	59.42	58.63	80.94	80.89
10	63.59	62.81	83.43	88.16
11	68.83	86.01	86.18	91.58
12	83.20	81.89	90.89	99.23

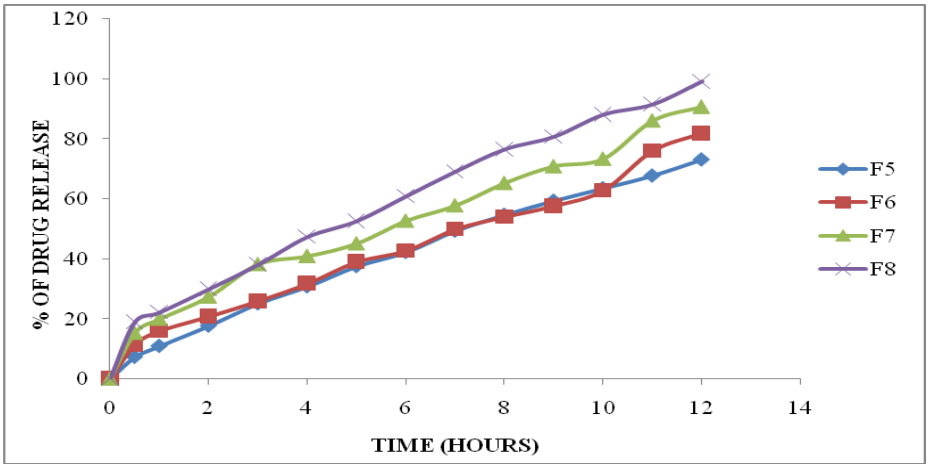


Fig 8.4: Dissolution profile of Azithromycin (F5- F8 formulations)

Table 8.8: Dissolution Data of Azithromycin Tablets Prepared With Karaya gum

TIME (hr)	CUMULATIVE PERCENT DRUG DISSOLVED			
	F9	F10	F11	F12
0	0	0	0	0
0.5	8.28	11.31	15.12	18.92
1	11.92	15.96	19.59	22.19
2	15.68	21.81	28.46	29.94
3	22.16	26.93	38.24	38.09
4	28.81	32.86	40.99	48.36
5	32.58	39.98	45.16	52.65
6	39.22	45.81	52.88	61.91
8	42.58	49.88	58.82	68.15
8	54.81	56.99	65.38	85.58
9	59.43	59.63	80.95	80.89
10	64.56	63.81	83.41	86.16
11	68.89	88.01	86.54	90.58
12	83.25	81.89	92.43	96.23

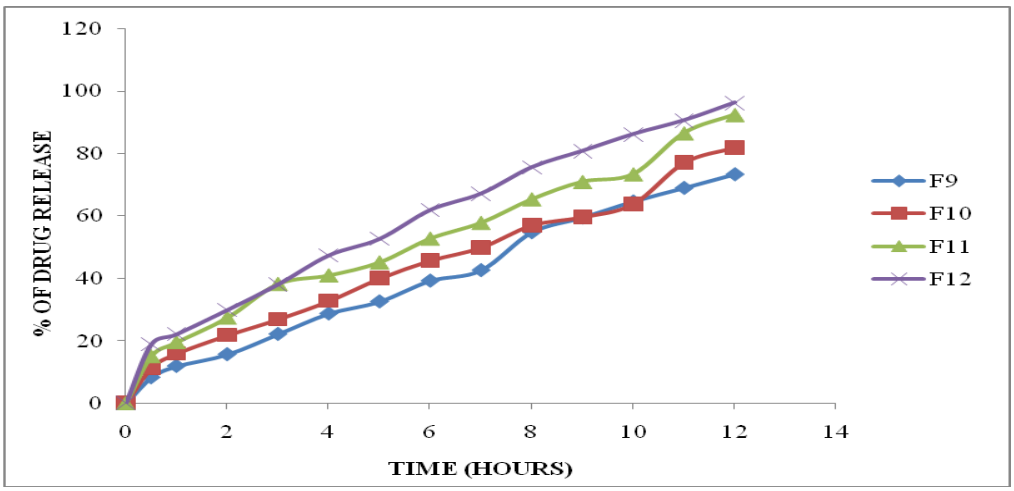


Fig 8.5: Dissolution profile of Azithromycin (F9- F12 formulations)

From the dissolution records it as obtrusive that the formulations organized with Acacia as polymer had been retard the drug launch up to desired time duration i.E., 12 hours and proven most of (F1) 98.percent in 12 hours with unique retardation.

Formulations organized with Pectin retarded the drug launch in the interest of a hundred and twenty mg (F8 Formulation) tested required launch sample i.E., retarded the drug launch up to 12 hours and tested maximum of two .23 % in 12 hours with right retardation.

Formulations organized with gum retarded the drug launch within the awareness of one hundred twenty mg (F12 Formulation showed required launch sample i.E., retarded the drug release as a good deal as 12 hours and confirmed most of .23 % in 12 hours with precise retardation.

From the above penalties it grew to become into evident that the approach F8 is magnificent device with liked drug launch sample extended as tons as 12 hours.

Application of Release Rate Kinetics to Dissolution Data:

Various models were tested for explaining the kinetics of drug release. 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.

Table 8.8: Release Rate Kinetics to Dissolution Data

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM% RELEASE	PEPPAS log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
18.92	0.5	0.808	1.288	-0.301	1.909	38.840	0.0529	-0.823	81.08	4.642	4.328	0.313
22.19	1	1.000	1.346	0.000	1.891	22.190	0.0451	-0.654	88.81	4.642	4.269	0.382
29.94	2	1.414	1.486	0.301	1.845	14.980	0.0334	-0.524	80.06	4.642	4.122	0.519
38.09	3	1.832	1.581	0.488	1.892	12.698	0.0263	-0.419	61.91	4.642	3.956	0.686
48.36	4	2.000	1.685	0.602	1.821	11.840	0.0211	-0.325	52.64	4.642	3.848	0.894
52.65	5	2.236	1.821	0.699	1.685	10.530	0.0190	-0.289	48.35	4.642	3.618	1.024
60.91	6	2.449	1.885	0.888	1.592	10.152	0.0164	-0.215	39.09	4.642	3.394	1.248
69.15	8	2.646	1.840	0.845	1.489	9.889	0.0145	-0.160	30.85	4.642	3.136	1.505
86.58	8	2.828	1.884	0.903	1.380	9.581	0.0131	-0.116	23.43	4.642	2.861	1.880
80.89	9	3.000	1.908	0.954	1.284	8.988	0.0124	-0.093	19.21	4.642	2.688	1.963
88.16	10	3.162	1.945	1.000	1.083	8.816	0.0113	-0.055	11.84	4.642	2.289	2.362
91.58	11	3.318	1.962	1.041	0.926	8.325	0.0109	-0.038	8.43	4.642	2.035	2.606
99.23	12	3.464	1.998	1.089	-0.114	8.269	0.0101	-0.003	0.88	4.642	0.918	3.825

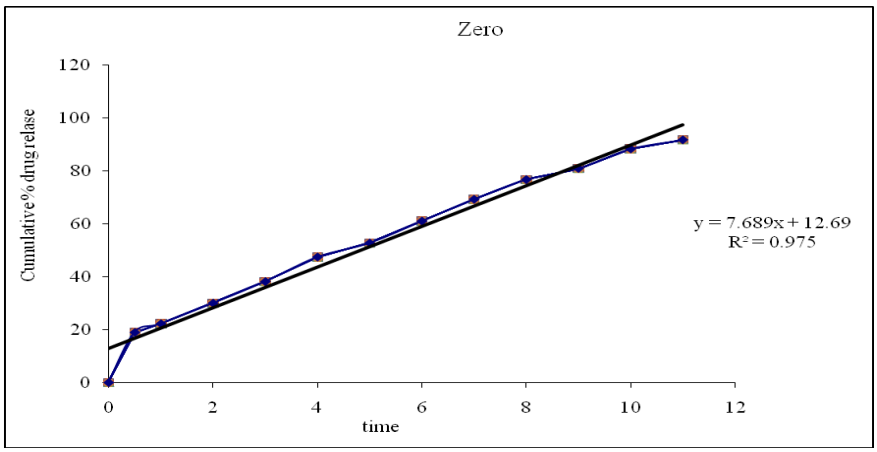


Fig 8.6 : Zero order release kinetics graph

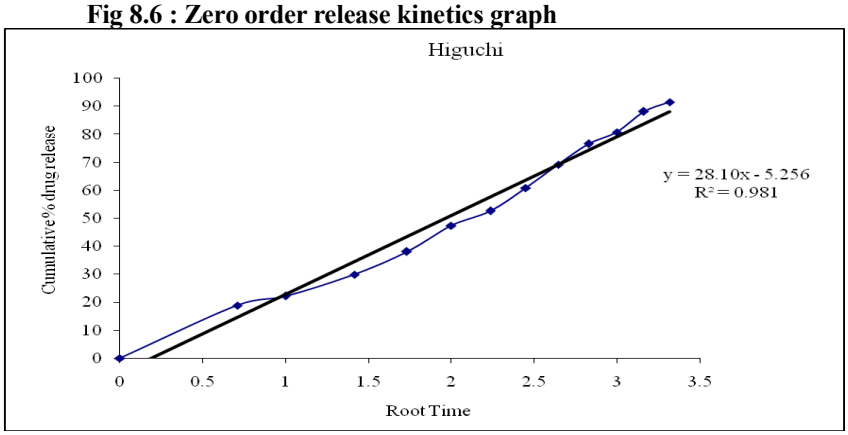


Fig 8.8: Higuchi release kinetics graph

From the above graphs it was evident that the formulation F8 was followed Zero oreder and Kors mayer Peppas release kinetics.

CONCLUSION:

The study was conducted two with the intention of formulating two and two comparisons of the sustained matrix pill using the Acacia, Pectin and polymer gum as a retarding agent. Of the two, the two mentioned above, two penalties and discussion, two are two concluded two than two the Pectin-containing sustained release matrix tablet method, which are considered excellent or optimized aspects. because it meets all two requirements of two of the two sustained release matrix tablets.

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