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"FORMULATION AND EVALUATION OF BI-LAYER SUSTAINED RELEASE TABLET OF AZITHROMYCINAND DOXYCYCLINE DRUG IN COVID-19 TREATMENT"

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ABSTRACT:

SARS-CoV-2, a novel corona virus, has caused an outbreak of COVID-19, a highly infectious pandemic that has complex viral pneumonia. Patients with risk factors are more likely to acquire secondary infections, which necessitate the use of antibiotics. However, drug repurposing initiatives have led to the recognition of antibiotics' roles outside of infection treatment. The current study looked at two medicines, azithromycin and doxycycline, and their antiviral, immunomodulatory, and distinctive pharmacokinetic profiles. It summarises current clinical trials as well as concerns about these medications' safety. Azithromycin has good lung tissue penetration, wide antibacterial action, and antiviral potential against COVID-19. It also demonstrated benefit when combined with other antiviral drugs in limited clinical studies, however many physicians are concerned about cardiovascular risk in sensitive individuals. Doxycycline is an essential antibiotic used to treat pneumonia. It has several benefits, including cardiac safety, simple access to lung tissue, antiviral potential, and immunomodulation effects via several channels. The pharmacological properties of these drugs suggest that more investigation into their usage in the treatment of COVID-19 is possible. The COVID-19 illness, which has no known cures or therapies, has wreaked devastation on mankind and gone beyond and beyond what has ever been seen before. The review discusses the possible therapeutic applications of Doxycycline in COVID-19 treatment, as well as the potential negative repercussions of repurposing the antibiotic in terms of antimicrobial resistance. Background Because of its antibacterial, anti-inflammatory, and antiviral properties, azithromycin could be utilised to treat COVID19. In mild-to-moderate disease, there are no randomization data. We wanted to see if azithromycin may help persons who had mild-to-moderate infections avoid being admitted to the hospital. COVID-19. Covid is a young man of 19 years. More factors will emerge as the illness worsens day after day. Corid-19 is 100% pure. One does not exist. Researchers nowadays may be found all around the globe. A global outbreak was proclaimed by the World Health Organization in 2020. are making an effort To some degree, this combination can be used as a solution for (AZI) and (DOXY).

Keywords: Bi-layer tablet, Sustained release tablet, Azithromycin, Covid-19, Doxycycline, SARS-CoV-2, Omicron, Nongonococcal urethritis, Epidemic, Delta.

INTRODUCTION:

Dosage Forms :-

Dosage forms (also called unit doses) are pharmaceutical drug products in thespecified forms in which they are marketed for administration and consumption, with aparticular mixture of active ingredients and inactive substances (excipients), in a particular configuration and apportioned into a particular dose. The term dosage form can also sometimes refer only to the pharmaceutical formulation of a drug product's included drug substance(s) and the various blends involved if any, without consideringother factors (such as how it is finally configured as a consumable and administrable product such as a tablets, patch, etc.). Because of certain vague boundaries and unclear overlap and misunderstanding of these terms and particular variants andqualifiers within the pharmaceutical companies and factories, caution is advised when conversing with people who might be unfamiliar with another person's use of this term.

Depending on the method, route of administration and also patient compliance dosage forms come in several types and varieties. Dosage forms are of mainly three types liquid, solid, and semisolid dosage forms. Common dosage forms include pills, tablets,capsules, syrups, etc. The route of administration (ROA) for drug delivery also dependson the dosage form of the substances. A liquid dosage form is the liquid form of the pharmaceutical product used as a drug or medication intended for administration or consumption.

Various dosage forms are present and available for a single particular drug, since different medical conditions can demand different routes of administration. For example, nausea, especially with vomiting makes it difficult to use an oral dosage form,and in such a case, it may be better to use an alternative route of administration such asinhalational, buccal, sublingual, nasal, suppository or parenteral instead. Additionally. a particular dosage form may be necessary for certain kinds of drugs, as there may be problems with various factors like chemical stability or pharmacokinetics.

Pharmaceutical Solid Dosage Form:

The most often utilised dose forms are solid dosage forms. Oral medications are given to patients in a number of ways. The oral route of medication administration is the most common way to deliver drugs with systemic effects. Because it is non-invasive, easy, and cost-effective, medication delivery via the oral route is often used. Often, the patient does not need to be admitted to the hospital, allowing him or her to resume normal activities with minimum disruption. Unlike many other doses that require significant knowledge to deliver, solid dosage forms require practically no expertise to administer. Powders, cones, lozenges, pills, cachets, capsules, and tablets are all examples of solid medications that may be taken orally. Even in the case of sustained action preparations that technically contain the equivalent of several normal dosages of drugs, these dosage forms contain a quantity of drug administered as a single unit and are known as solid dosage forms collectively. The safest and least expensive route is usually the most convenient oral route. It's the most commonly used. However, because of the way medication travels through the digestive tract, it has limitations. For orally administered drugs, absorption may begin in the mouth and stomach, but the small intestine absorbs the majority of the drug. The drug passes through the intestine wall, where it is chemically altered (metabolised) by the liver, which reduces the amount of drug that reaches the bloodstream. As a result, when such medications are injected directly into the bloodstream, they are frequently given in fewer amounts to provide the same effect (intravenously). If the tablet releases the medicine quickly, the blood level of the drug may become excessively high, resulting in an overreaction. Toxicity levels may be increased as a result of excessive drug release. If the medicine is not released from the tablet, it is expelled from the face without being absorbed. Medicine manufacturers must design their tablets in such a way that the drug is released at the desired rate.

Tablets are the solid dosage form containing medicaments with or without excipients.

Physicochemical characteristics are necessary to consider before deciding tablet formulation

of the respective drug or drugs. Tablets are prepared by compressing a drugwith or without diluents. So before attempt to develop an oral delivery system it is necessary to have a basic understanding and some knowledge of the following aspects:-

1. Physicochemical, pharmacokinetic and pharmacodynamics characteristic of the drugs.

2. The automatic and physiological characteristics of GIT, and

2. Physiological characteristics and the drug delivery mode of the dosage form to be Designed.

Anatomic and physiological characteristics of the GIT

Region	Surface Area(m^2)	pH of the region	Transits Time	
			Fluid	Solid
Stomach	0.1-0.2	1-3.5	50 min	8 hrs.
Small Intestine	4500	5-7.5	2-6 hrs.	4-9 hrs.
Large Intestine	0.5-0.10	6.8	2-6 hrs.	3 hrs. to 3 days

Tablet Dosage Form:

Tablets, the most common oral dosage form, are unit dosage forms containing one or more active ingredients along with excipients and prepared by compression powder orgranules into a definite shape using punches. Tablets are popular because of accurate dosage, better physical- chemical stability in comparison with liquid dosage forms, economical production and elegant appearance thus making them acceptable to user. On the other side, tablets and capsules presently account for more than two thirds of thecomplete price of drugs generated worldwide.

Ideal Properties of Tablets:

1. A tablet should have elegant product identify while free of defects like chips,cracks, discoloration, and contamination.
2. During its manufacturing packaging, shipping and dispensing, it should haveadequate power to resist mechanical shock.
3. In order to preserve the physical characteristics over time, it should havephysical and chemical stability.

4. The tablet must be able to predictably and reproducibly release the medicinalagents.
5. It must have a chemical stability over time so as not to follow alteration of themedicinal agents.

Advantages:

1. They are unit dosage form and offer the greatest compatibilities of all oral dosage form for greatest dose precision and least content variability.
2. Cost is lowest of all oral dosage form.
3. Lighter and compact.
4. Easiest and cheapest to package and strips.
5. Easy to swallowing with less tendency for hung-up.
6. Enteric coating is feasible to maintain the release product.
7. The coating method can mask objectionable odour and bitter taste.
8. Suitable for manufacturing on a big scale.
9. Maximum chemical and microbial stability over any type of oral dosage.

Identification of the product is simple and quick, requiring no further stepwhen using a punch face embossed and/or monogrammed.

DRUG PROFILE:

Azithromycin (API):

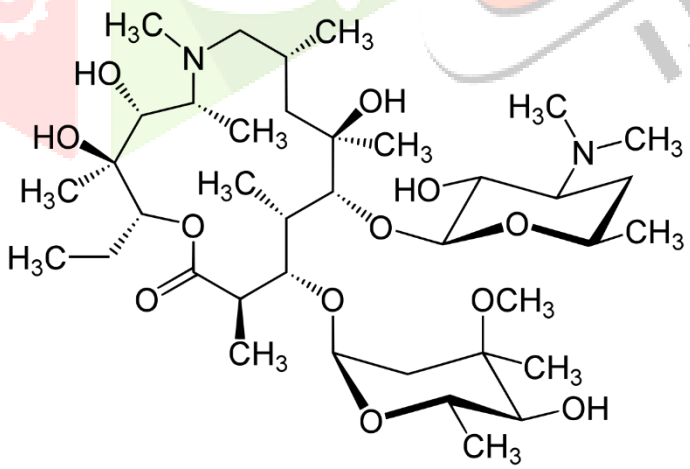


Fig No.1 chemical structure of Azithromycin

Molecular Formula: $C_{38}H_{72}N_2O_{12}$

Molecular Weight: 749.0

IUPAC Name: (2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-15-oxo- 11-{[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy}-1-oxa-6-azacyclopentadec-13-yl 2,6-dideoxy-3C-methyl-3-O-methyl-α-L-ribo-hexopyranoside

Melting Point: 113-115°C

Category: Azithromycin belongs to the class of drugs known as macrolide antibiotics. It works by killing bacteria or preventing their growth.

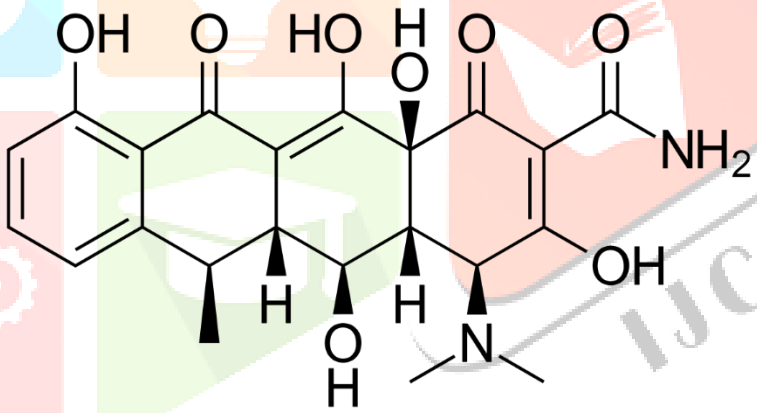
Half Life: 68 hours

pH: **6.0-7.2**

solubility: Azithromycin is soluble in organic solvents such as ethanol, DMSO, and dimethyl formamide (DMF). The solubility of azithromycin in ethanol and DMF is approximately 16 mg/ml and approximately 5 mg/ml in DMSO. Azithromycin is sparingly soluble in aqueous buffers methanol.

Appearance: white crystalline powder

B) Doxycycline (API):



Chemical structure of Doxycycline

molecular formula: $C_{22}H_{24}N_2O_8$

molecular weight: 512.94

IUPAC Name: IUPAC name (4S,4aR,5S,5aR,6R,12aS)-4-(Dimethylamino)-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide.

Melting Point: 212-219 ^{0} C

Category: Doxycycline belongs to the class of medicines known as tetracycline antibiotics.

Half Life: 20 hours

pH : 2.16.

Solubility:

This product is soluble in water (50 mg/ml), yielding a clear, yellow-green solution. Mild warming may be required to fully dissolve the material. This product is also reported to be soluble in methanol, sparingly soluble in ethanol, and insoluble in chloroform or ether.

Appearance: yellow crystalline powder.

- **Excipients-**

I. Disintegrating- Croscarmellose.
II. Superdisintegrant- Sodium starch glycolate.
III. Absorb moisture- Talcum.
IV. Good adhesive properties- PVP K 30.
V. Increased hardness – Aerosil.
VI. Binder/Diluent - Microcrystalline cellulose.
VII. Flow agent- Magnesium stearate.
VIII. Excellent compressibility properties- Lactose.
IX. Binder or matrix former- CMC/Carboxymethel cellulose.

Material and Method :

Equipment used:

FTIR

Make: jasco FT/IR

Software: OPUS 7.5

Attachment: Transmitter, ECO-ATR

UV Spectrophotometer:

Specifications of double beam UV-Visible spectrophotometer

Make: Jasco Model: V-630

Software: Spectra Manager, UV Probe 2.51

Analytical balance:

Make: Shimadzu

Model: BL-22011

Ultrasonicator:

Make: Citizen digital ultrasonicater cleaner

Model: CD-4820

Appearance and colour-

1) Azithromycin – White crystalline powder, odourless powder.

2) Doxycycline – light-yellow crystalline powder, odorless powder.

Details of Drug sample

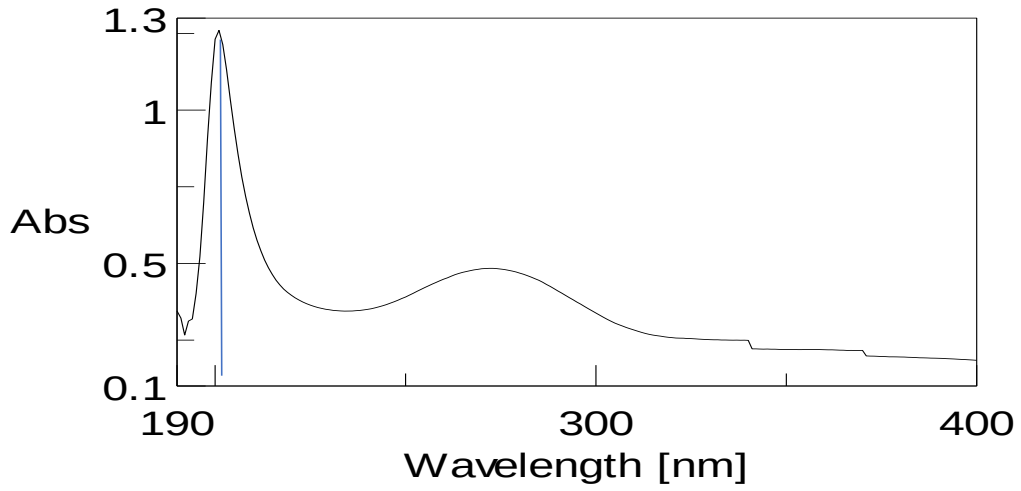
	Name of Drug		Quantity	Drug Supplier
1	**Azithromycin**	I.P	20g	Ozone International Pvt.
2	**Doxycycline**	I.P	20g	Ozone International Pvt.

Melting point determination:

Melting point of Azithromycin and Doxycycline was determined using capillary tube method. Observed value of melting points of the two drugs was compared with the reported values.

Sr. No.	**Melting PointRange**	**AZITHROMYCIN(API)**	**DOXYCYCLINE(API)**
1.	Asper Literature	113^0-115^0 C	212-219 ^{0} C
2.	**Practical**	**115^0 C**	**214^0 C**

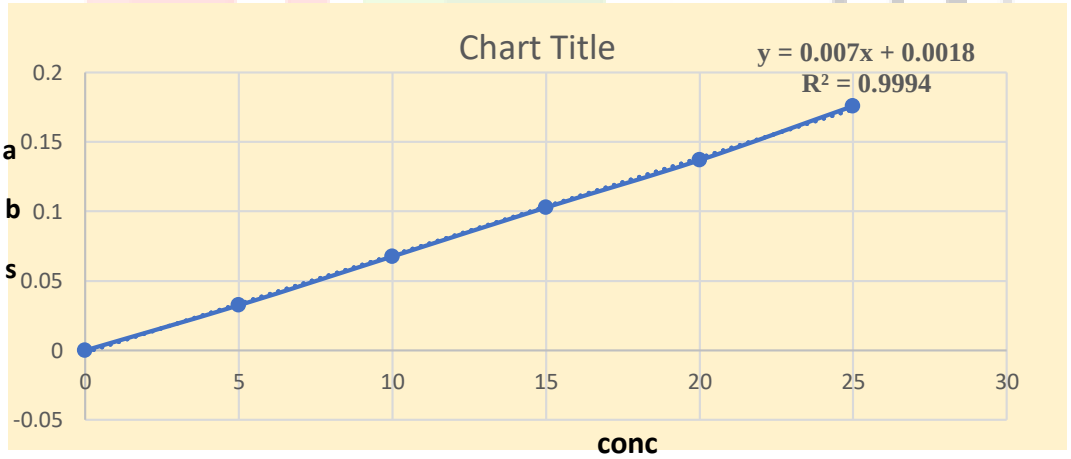
UV spectrum of Azithromycin:



λ_{max} of azithromycin-210 nm

UV Calibration Curve of Azithromycin:

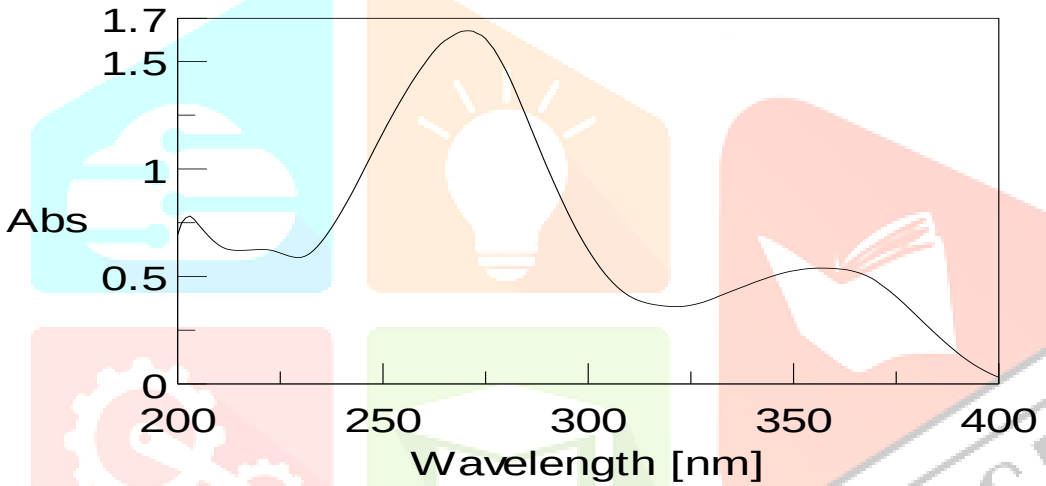
Sr. No.	Concentration (µg/ml)	Absorbance
1.	0	0
2.	5	0.03245
3.	10	0.06757
4.	15	0.102797
5.	20	0.136824
6.	25	0.175807



Sr. No.	Solvent	Equation	R^2
1.	Methanol	y = 0.007x + 0.0018	0.9994

Ultraviolet Absorbance Spectrum - Doxycycline :

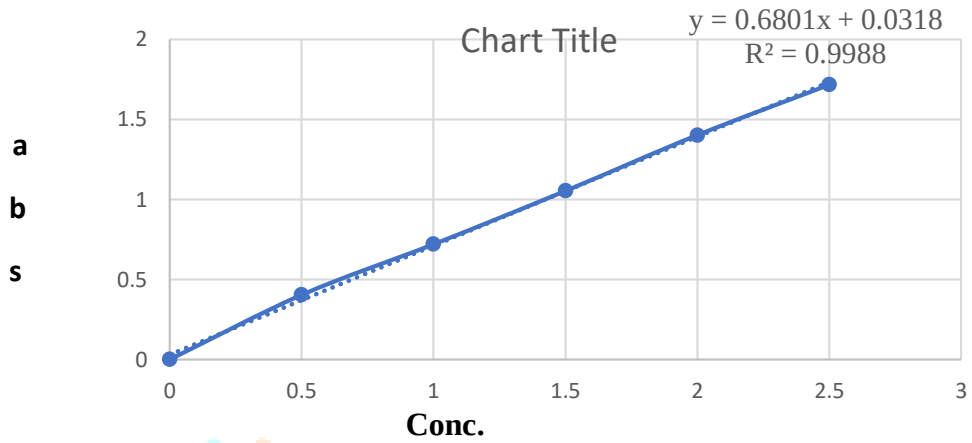
Sr. No.	Concentration (µgm/ml)	Absorbance
1	0	0
2	2	0.4035
3	4	0.7595
4	6	1.0526
5	8	1.3511
6	10	1.7153



λ_{max} of Doxycycline -275 nm

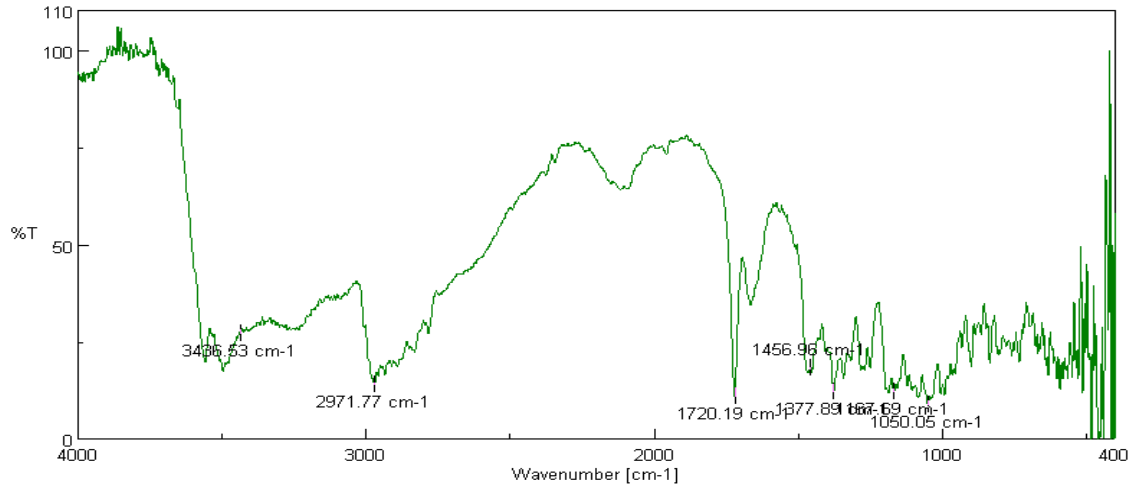
Calibration Curve of Doxycycline in Methanol at various concentration-

Standard curve of Doxycycline in Methanol-



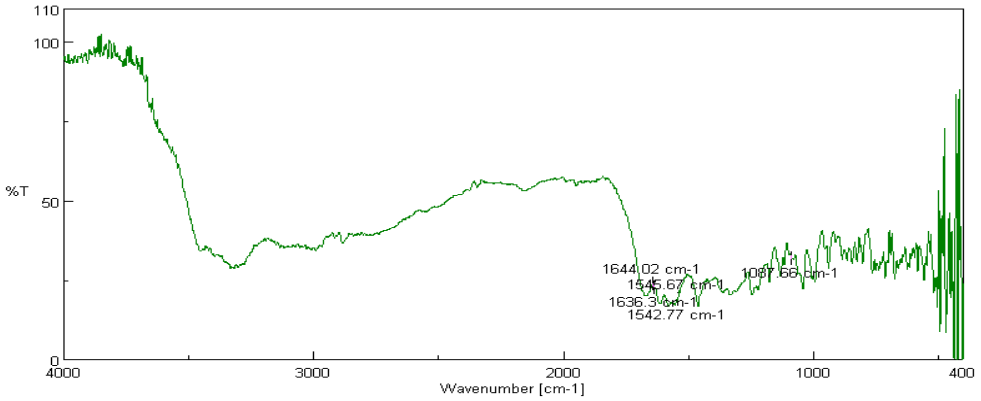
Sr.no	Solvent	Equation	R^2
1.	Methanol	y = 0.6801x + 0.0318	R^2 = 0.9988

Infrared Spectrum of Azithromycin-



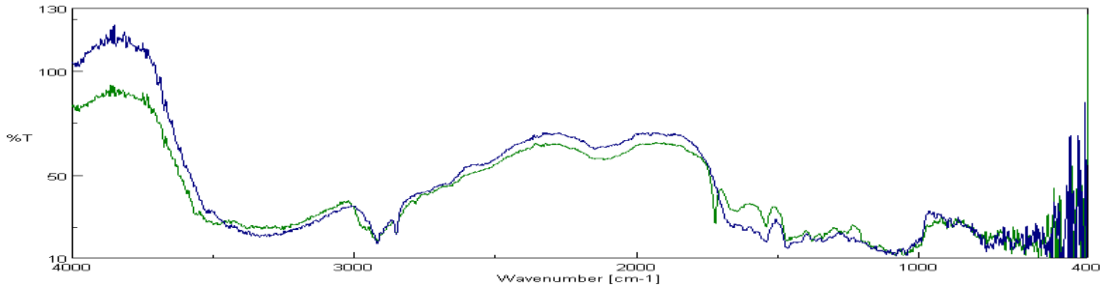
Sr. No.	Inference	Wave Number (cm^{-1})
1.	OH stretching (intermolecular hydrogen bonding)	3436.53
2.	C-H Stretching vibration	2971.77
3.	C= O carbonyl ester Stretching	1720.19
4.	CH3-O	1456.96
5.	CH2-O	1377.89
6.	C-O-C	1050.05

Infrared Spectrum of Doxycycline –



Sr.no	inference	Wave Number (cm^1)
1	C=O Stretching	1644.02
2	N-H Bending and C-N Stretching	1545.67
3	B-plated sheet structure	1636.3
4	C-O-C	1087.66

IR peak value of Azithromycin and Doxycycline Mixture with Polymers :



Types of Bonds	Wave Number /cm^{-1} Found
N-H Stretching	**3456.78**
C-H Stretching (Methyl)	**2970.8**
C-H Stretching Vibration of (aromatic ring)	**3114.47**
C=O Stretching Vibration of Amide Moiety	**1650.77**
Aliphatic C-H Stretch	**2962.13**
CH2 (Bending)	**1461.78**
C=C Stretching/bending	**1599.66**
COOH bending	**1381.75**
Disubstituted benzene	**1696.09**

EVALUATION OF GRANULES:

Wet granulations:

Granulation is the process of collecting particle together by creating bonds between them. When the required homogeneity, compatibility or flow ability of powder cannot be obtained by simple mixing, the ingredient must be granulated prior to compression.These are several reasons for using the granulation process (wet/dry) including the following. The wet granulation technique uses the same preparatory and finishing steps(screening or milling or mixing) as the two previously discussed granulation techniques. The special portions of wet granulation technique involve the wet massing of the powders, wet sizing or milling, and also involves drying. Wet drying is a process or technique in which a liquid is added to a powder in a vessel or an equipment with any type of force provided gives or produce agglomerates or granules. In wet granulation technique, the bonding properties of the liquid binders used in the formulation are generally enough to produce bonding's with minimum of additives used.

- Improving powder flow ability.
- Improving content uniformity of API's. in dosage form to assure consistency of dosing.
- Improving the bioavailability of some API's.
- Taste masking of poor taste API's/ improvement in palatability.
- Material densification. Compatibility and compressibility enhancement of theAPI's.
- Drug release control.
- Reduction of dust, and Improvement in tablet physical properties.

Wet granulation is a technique which involves that a specific liquid binder is addedto the powder blend and granules are produced by agitation.

Characterization of Granules of API and Excipients:

For each type of preliminary formulation blends, blends of API and Excipients were prepared and evaluated for various parameters as explained earlier.

2. Angle of Repose (θ):

The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius of the heap (r) was measured and the angle of repose was calculated using the following formula

$$\tan \theta = h/r$$

Therefore $\theta = \tan^{-1}(h/r)$

Where, θ = angle of repose, h = height of the cone, r = radius of the cone base

Bulk Density (pb):

Apparent bulk density (P_b) was determined by pouring blend into a graduated cylinder. The bulk volume (V_b) and weight of the powder (M) was determined. The bulk density was calculated by using the Following formula

$$P_b = M/V_b$$

Where, P_b = Bulk Density, M = Weight of sample in gm, V_b = Final volume of blend in cm

Tapped Density:

It is the ratio of total mass of the powder to the tapped volume of powder. The volume was measured by tapping the powder for 500 times. Tapping was done up to time there is no further movement of volume was noted. The tapped density was calculated by using the following formula [4]

$$P_t = M/V_t$$

Where, P_t = Tapped Density, M = Weight of the sample in gm, V_t = tapped volume of blend in cm

Carr's index or % compressibility

The simplest way for measurement of free flow of powder is compressibility, a indication of the ease with which a material can be induced to flow is given by compressibility index (I) which was calculated as follows: [4]

$$I = P_t - P_b / P_t \times 100$$

Where, I = Carr's index or % Compressibility, P_t = Tapped density, P_b= Bulk density

Hausner's ratio

Hausner's ratio is an indirect index of ease of powder flow. It was calculated by the following formula

Hausner's ratio = P_t/P_b

Where, P_t = Tapped density, P_b = Bulk Density

Evaluation of Tablet Parameters:

Compressed tablets were evaluated for following parameters

Precompression studies- Azithromycin:

Formulation Code	Bulk Density	Tapped Density	Carr's Index (%)	Housner's Ratio (%)	Angle of Repose(Degree)
F1	0.06944	0.08333	20	1.200	37.81
F2	0.06957	0.08346	19	1.199	37.89
F3	**0.06933**	**0.08311**	**20**	**1.198**	**37.99**
F4	0.06947	0.08341	20	1.200	37.55
F5	0.06940	0.08344	19	1.202	37.91

Precompression studies- Doxycycline.

Formulation Code	Bulk Density	Tapped Density	Carr's Index (%)	Housner's Ratio (%)	Angle of Repose (Degree)
F1.	0.072	0.097	25.77	1.3472	36.99
F2.	0.072	0.097	25.77	1.3472	36.89
F3.	**0.072**	**0.098**	**26.53**	**1.3611**	**37.96**
F4.	0.073	0.097	25.77	1.3287	37.54
F5.	0.071	0.096	26.04	1.3521	37.95

Compositions of Bi-layer Tablets Sustained Release Layer of Azithromycin:-

Sr.No	Ingredient	F1(mg)	F2(mg)	F3(mg)	F4(mg)	F5(mg)
1	Azithromycin	250	250	250	250	250
2	Carboxymethylcellulose/CMC	6	6	9	9	6

Compositions of Bi-layer Tablets Sustained Release Layer of Doxycycline:

Sr.No	Ingredient	F1(mg)	F2(mg)	F3(mg)	F4(mg)	F5(mg)
1	Doxycycline	100	100	100	100	100
2	Carboxymethylcellulose /CMC	10	10	8	9	9
3	PVP K30	6	11	2	4	11
4	Starch	26	24	25	25	26
5	Lactose	9	7	8	6	8
6	Magnesium sterate	9	9	6	9	6
7	Talcum	15	14	15	15	15
8	p.water	Q.S	Q.S	Q.S	Q.S	Q.S
	Total weighat	175	175	175	175	175

Prepared Bi-layer tablets of Azithromycin and Doxycycline:

Evaluation of

Compressed Tablets:

All the tablet formulation were subjected for Organoleptic, Physical and Chemical evaluation as shape. Thickness, Hardness, Friability, Weight Variation, In-vitro Disintegration Time, Drug Content, And In-vitro Dissolution Studies.

Appearance:

The size and shape of the tablets can also effect the disintegration time and subsequent dissolution profile. In general, a smaller tablet in terms of mass has a faster disintegration time than larger tablets, all other factor being equal. Similarly, a tablets shape with more surface area generally was a faster disintegration time than a tablet shape having less surface area, all other factor being equal. Randomly picked tablets from each formulation batch examined for shape and in presence of Light for color. Tablets showed Cylindrical shape and pale yellowish in color.

Weight Variation :

The percent weight variation for all the formulation batches are tabulated in Table. the entire tablet weight variation test as the % weight variation was within the Pharmacopoeia contents of 5%. The weight of tablet was found to be uniform Uniformweight due to the uniform die fill with acceptable variations as per USP standard wereobtained since blend of material was free-flowing.

Hardness :

Tablet crushing strength, the critical parameter was controlled as the resistance of abletsto capping, abrasion are breaking under the condition of storage, transportation and handling before usage depends on its hardness. Hence, hardness for all optimized batches is tabulated in Table was measured using the dial hardness tester (Monsanto Hardness Tester).

Thickness :

Tablet thickness can be measured using a simple procedure. Three tablets were taken and their thickness was measured using Vanier calipers. The thickness was measured by placing tablet between two arms of the Vanier calipers. The values are shown in Table.

Friability :

The friability of a sample of 20 tablets was measured utilizing a USP type Roche Friabilitor. Pre-weighed tablets were placed in a plastic chambered Friabilitor attachedto the motor revolving at a speed of 25 rpm for 4 min. the tablets were then de-dusted, teweighted, and percentage weight loss (friability) was calculated following by equation.

$$\% \text{ Friability} = W_{initial} - W_{final} / W_{final} \times 100$$

Wi=Initial Weight of 20 tablets.

Wf=Weight of 20 tablets after 100 revolutions.

The % friability values for all formulations batches are tabulated.

Drug Content:

The drug content of all formulations was calculated by UV spectrophotometric methodby quantization mode. Drug content for all batches are tabulated in Table threetrials from each formulations were analyzed spectrophometrically. The mean value andstandard deviation of the all formulation were calculated. The drug content of the mbletwas found between range i.e. Azithromycin 95.20% to 99.15% and Doxycycline 95.81% to 99.27%. The results indicate that in all the formulations. the drug content was uniformed. The cumulative drug release by cach tablet in the in vitro release studied was based on the mean content of the drug present in the respectivetablets:

In-vitro Disintegrating Time:

Disintegration is first important for drug absorption from a solid dosage form after oral administration was preliminary focused. An important factor affecting the disintegration is the tablets hardness and/or the compaction force used in making the tablet hardness. The hardness of tablets has an influence on the disintegration time as itaffects the porosity of the matrix and, accordingly, the ability of water to penetrate through the compact core. All tablets disintegrate rapidly without disc in the IP test especially when used at optimum concentration of selected superdisintegrant. The sodium starch Glycolate was used as superdisintegrant in different concentration in formulations. In-vitro disintegration time for all formulated batches it showed that the sodium starch Glycolate shows better disintegration time. Hence it was evident that selected superdisintegrant for study played vital role in disintegration behavior. As discussed above, difference in the particle size generated inthe Disintegrate tablets could affect drug dissolution since breaking tablets into finer fragments may promote drug dissolution by providing larger total surface areas for drugdissolution to takes place. Drug percent dissolved at 62 mins. to 115 mins for formulatedbatches.

Dissolution Test:

The dissolution was carried out according to the procedure obtained from IP as well asthe research articles. The pH 6.8 phosphate buffer solution was prepared. Buffersolution thus prepared was kept form achieved temperature 37°C. The tablets were subjected to dissolution as the batches were formulated. The sample was withdrawn at

0. 60, 120, 180, 240, 300, 360, 420 min. interval in an amount 2 ml; equal amount was replaced by fresh medium maintained at same condition. The dissolution was analyzedin UV for the presence of drug Azithromycin at 210nm and Doxycycline at 275 nm. This procedure followed for all formulations.

Evaluation of Formulated Batches-

Sr.No	Formulations	Thickness (mm ± SD)	Hardness (kg/cm^2)	Friability(%)	Weight Variation(mg±SD)
1	F1	3.37±0.90	4.81±0.155	0.57±0.82	497± 0.75
2	F2	3.63±0.95	4.50±0.142	0.45±0.86	494± 0.50
3	**F3**	**3.88±0.92**	**5.19±0.140**	**0.61±0.82**	**503± 0.75**
4	F4	3.54±0.96	4.38±0.143	0.71±0.83	498± 0.50
5	F5	3.43±0.95	4.73±0.150	0.41±0.85	496 ±0.50

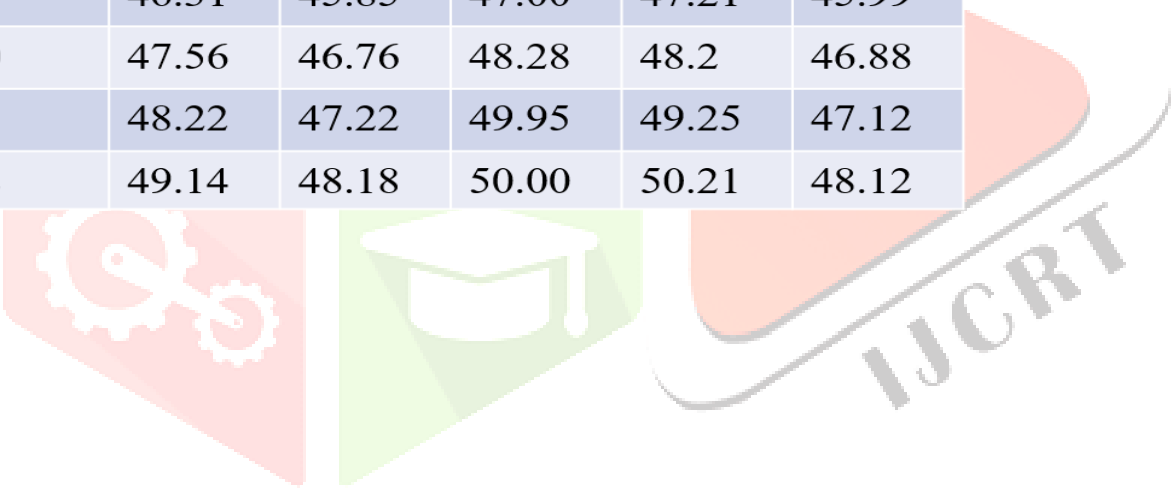
Disintegration time-

Formulation Code	Disintegrating time (min)
F3	120

Comparative % Drug Release of Batches (Azithromycin)

Time Min& Hr.	% Of drug release				
	F1	F2	F3	F4	F5
45 m	6.21	6.14	7.02	6.22	7.00
1	9.00	8.00	9.00	9.21	8.99
2	12.78	11.08	12.15	11.25	9.66
3	16.32	15.02	16.98	15.36	12.22
4	20.2	18.2	21.28	20.00	16.00

12	**39.56**	**36.26**	**40.56**	**40.00**	**38.00**
13	40.00	38.00	41.23	41.21	39.00
14	41.23	40.83	42.45	42.21	40.78
15	42.55	41.50	43.23	43.25	42.1
16	43.00	42.00	44.00	44.23	43.26
17	44.21	43.20	45.30	45.21	44.23
18	45.31	44.30	46.12	46.32	45.26
19	46.31	45.85	47.00	47.21	45.99
20	47.56	46.76	48.28	48.2	46.88
21	48.22	47.22	49.95	49.25	47.12
22	49.14	48.18	50.00	50.21	48.12



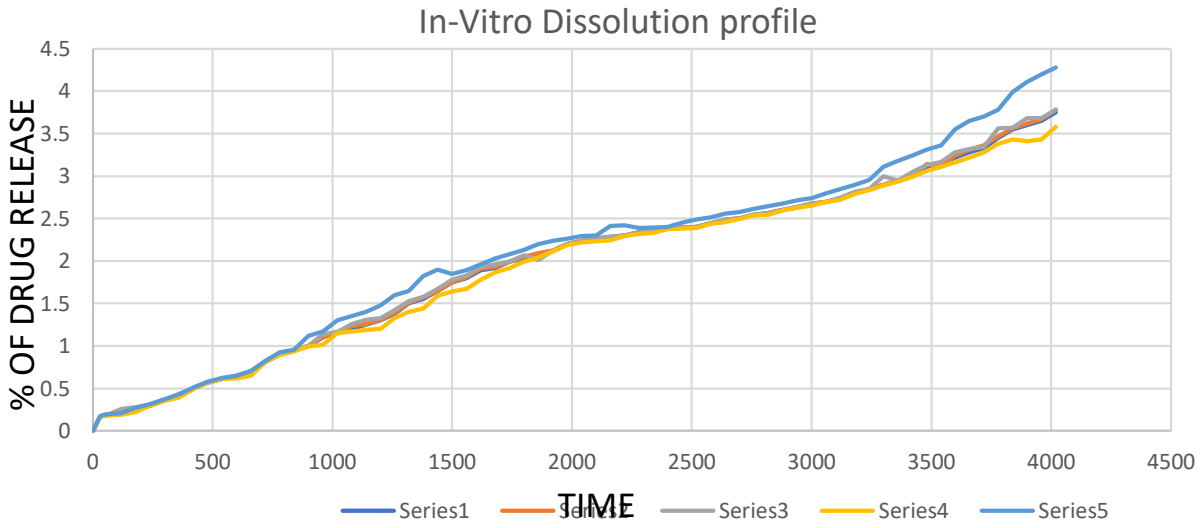
36	**63.00**	**62.21**	**64.22**	**64.41**	**64.23**
37	64.55	63.14	65.22	65.23	65.26
38	65.9	64.75	66.32	66.10	66.32
39	66.2	65.23	67.65	67.22	67.25
40	67.00	66.53	68.25	68.32	68.32
41	68.12	67.53	69.22	69.32	69.32
42	69.12	68.22	70.21	70.25	70.21
43	70.00	69.32	71.25	71.24	71.51
44	71.12	70.00	72.56	72.27	72.32

23	50.0	49.55	51.66	51.11	49.55
24	51.22	50.00	52.13	52.00	50.36
25	52.31	51.20	53.22	53.14	51.24
26	53.12	52.00	54.25	54.21	52.21
27	54.12	53.45	55.36	55.21	53.26
28	55.23	54.65	56.85	56.85	54.21
29	56.12	55.14	57.36	57.33	55.23
30	57.41	56.2	58.17	58.9	56.10
31	58.22	57.21	59.39	59.36	57.4
32	59.00	58.36	60.22	60.21	58.58
33	60.03	59.12	61.23	61.25	61.02
34	61.00	60.12	62.99	62.35	62.05
35	62.00	61.12	63.45	63.25	63.00
36	**63.00**	**62.21**	**64.22**	**64.41**	**64.23**
37	64.55	63.14	65.22	65.23	65.26
38	65.9	64.75	66.32	66.10	66.32
39	66.2	65.23	67.65	67.22	67.25
40	67.00	66.53	68.25	68.32	68.32
41	68.12	67.53	69.22	69.32	69.32
42	69.12	68.22	70.21	70.25	70.21
43	70.00	69.32	71.25	71.24	71.51
44	71.12	70.00	72.56	72.27	72.32
45	72.21	71.56	73.99	73.29	73.56
46	73.58	72.23	74.65	74.56	74.21
47	74.21	73.5	75.25	75.00	75.09
48	75.00	74.00	76.35	76.32	76.77

Dissolution profile- Azithromycin :

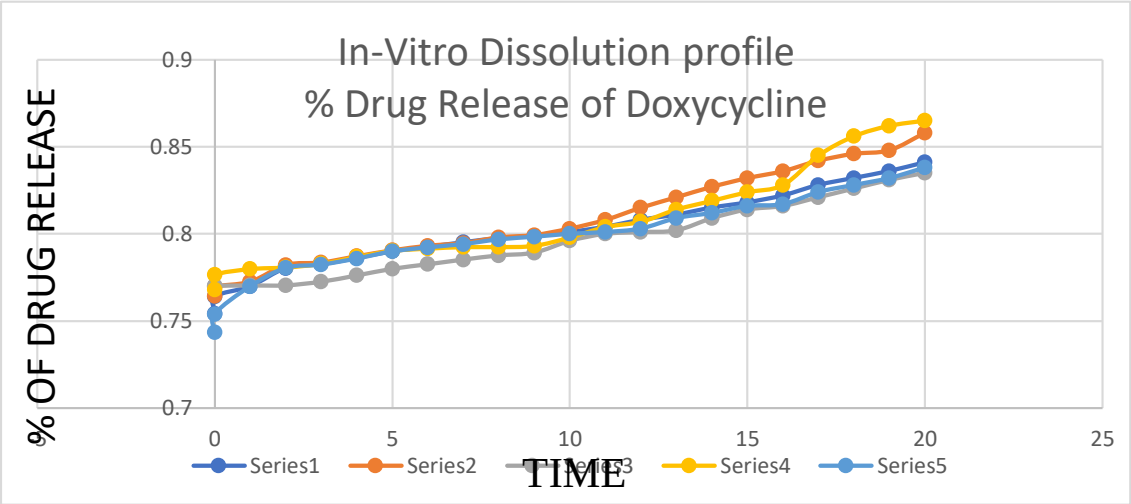
Time in min

Comparative Dissolution Profile of All Batches Azithromycin



in-Vitro Dissolution profile of SR- Doxycycline:

Time Hr.	% Of drug release				
	F1	F2	F3	F4	F5
0	0	0	0	0	0
1	0.99	0.86	1.10	0.92	0.90
2	5.4	4.9	10.98	0.96	0.93
3	9.5	9.00	16.79	1.02	1.00
4	14.8	13.2	21.14	6.3	5.3
5	18.19	17.3	26.12	11.04	10.02
6	22.00	19.22	30.82	17.43	14.12
7	27.21	27.18	34.00	22.21	18.19
8	32.56	32.00	38.52	27.63	23.00
9	37.44	36.00	42.11	32.37	28.56
10	42.11	40.00	46.23	37.54	33.88
11	46.11	46.00	50.43	38.44	38.38
12	50.88	49.99	54.14	42.00	43.00



Comparative Dissolution Profile of All Batches Doxycycline

Stability study-

Stability studies

Stability studies of the Best Formulation F3 was carried out by keeping the tablets at room temperature and 40°C +2° C/ 75 ±5% RH (stability chamber) for 30 days. From the stability studies it was found that formulation were stable at room temperature and 40°C +2° C/ 75 ±5% RH for a period of 60 days. There was no appreciable and highlighting change in physical properties, drug release and drug content during the testing period. Thus the test indicated stability of formulations.

1. Physical Appearance:

Color: unchanged.

Odour: unchanged.

Formulation	Study Conditions Specification	Months	Drugs Name	%Drug Content	%Drug Release
F3	40°C +2° C/ 75 ±5% RH	Initial	Azithromycin	98.58	96.40
			Doxycycline	98.72	94.22
		30 days	Azithromycin	98.21	96.40
			Doxycycline	98.44	94.22
		60 days	Azithromycin	97.73	96.40
			Doxycycline	97.84	94.22

Stability Parameters of F3 for 0, 30, 60 Days

Formulation Number.	Friability	Hardness (Kg/cm^2)	% Drug release	In-Vitro Disintegration time (min)
R3	0.522±0.028	5.7±0.10	95.10±0.05	122

SUMMARY AND CONCLUSION:

Summary:

- Oral route of administration is perhaps the most appealing route for the deliveryof drugs Various dosage forms are administered orally. The tablet is the one of the most preferred dosage forms as stability of tablets is more in comparison with oral liquids. Patient compliance is more for tablets than any other dosage forms.

- The bioavailability of drug is dependents on In-vitro disintegration, dissolution and various other evaluation parameters. The type of tablets formulated are bilayer sustained release tablets. The task to developing these tablets is accomplished by using a suitable binder, diluents and sustained releasing agent.

- In spite of several advantages in modern medicine and upcoming novel drug delivery system, the use of convectional tablet is still at its peak. No matter thatthe new and latest innovation has emerged in recent years but choice of bilayer tablets of Azithromycin and Doxycycline product will holds its position. The main criteria for formulation of such tablets is to treat pneumonia and covid-19 The doses of drugs in the bilayer tablet were taken as per the standard doses.

- The aim here was to formulate bilayer tablets with both layers (Azithromycin and Doxycycline) having sustained release profiles.
- The doses of drugs in the bilayer tablet were taken as per the standard doses.

- The formulation include Azithromycin and Doxycycline with excipients. Binder is

Starch, Crospovidone as disintegrant, as sustained release agent,magnesium stearate as lubricant, talc as glidant and lactose & Mannitol as filler.

- purpose 5 batches were formulated amongst which batch F3 showed best performance.
- Before this the Pre-formulation study was carried out for various aspects including Infrared analysis, Differential Scanning Colorimetry, UV- analysis, Physical Characterization etc.

- Biological Studies on wistar rats were done to check the antibiotics activity of Azithromycin when taken in combination with Doxycycline.

- The result revealed that the F3 batch showed the best performance.

- Sustained release Tablet (SR) of (AZI-DOX) were formulated successfully withdesired characteristics; disintegrated rapidly.
- Prepared SR will provide Rapid onset of action.
- Prepared SR will enhanced the patient's convenience and Patients compliance.
- The sustained-release tablet works at the right time.
- Prepared SR is shown better and Advanced formulation.

Conclusion:

- On the basis of the study, selection of drug candidate and the type of formulationlead to the formulation of Bilayer Tablets to treat pneumonia and covid-19 were formulated successfully.

- The addition of magnesium stearate which produce satisfactory results for flow property of powders.
- Addition of crospovidone improved drug release of Azithromycin layer.
- The Pre-formulation study revealed the purity of drug and also it confirmed the stability of drug with excipient hence proved to be compatible there.
- All the tablets formulation showed satisfactory results with respect to hardness, friability, disintegration time, drug content and In-vitro dissolution studies.
- The binder, filler, diluents, lubricants used in the formulations which improve the tablet quality and stained release agent improve the disintegration and dissolution property of tablet.
- The powder was granulated by wet granulation and the second layer wascompressed

above the compressed first layer, it is a good method used for the compression of bilayer tablets. Wet granulation is the best method for formulation of such bilayer tablets.

-
- The results obtained in Biological Studies revealed that the present drug combination shows antibiotics activity. Azithromycin does not hinders theantibiotics activity of Doxycycline when taken in combination. Thus, there is no Drug-Drug Interaction between Azithromycin and Doxycycline.

Therefore, this research work concludes the successful was shown the

"Formulation and Evaluation of Azithromycin and Doxycycline BilayerTablets for the Treatment of pneumonia and Covid-19"

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