International Standard Serial Number (ISSN): 2319-8141
International Journal of Universal Pharmacy and Bio Sciences 2(6)*: November-December 2013*
INTERNATIONAL JOURNAL OF UNIVERSAL PHARMACY AND BIO SCIENCES
*IMPACT FACTOR 1.89****
*ICV 5.13****
Pharmaceutical Sciences **RESEARCH ARTICLE……!!!**

FORMULATION AND EVALUATION OF BIPHASIC TABLETS OF AMOXICILLIN TRIHYDRATE MODIFIED RELEASE SYSTEM

Anand Rani P*, J.N Suresh, Ch. Ajay Babu, M.Venkataanjenelu
Department of Pharmaceutics, Narasaraopeta Institute of Pharmaceutical Science, Narasaraopeta, Guntur.

KEYWORDS:

Amoxicillin, Immediate Release, Extended Release, Bilayer Tablets, Antibiotics.

For Correspondence:

Anand Rani P *

Address:

Department of Pharmaceutics, Narasaraopeta Institute of Pharmaceutical Science, Narasaraopeta, Guntur.

ABSTRACT

The aim of the current investigation is to design bilayer oral tablet modified release dosage forms of amoxicillin trihydrate , in which one layer the drug is immediately released so that it gives an immediate action and the other layer is extended release which release the drug for a prolong period and match with theoretical drug release profile. Modified preparations where the rate and/or place of release of the active ingredient are different from that of the conventional dosage form administered by the same route. **Method:** Amoxicillin Trihydrate bilayer tablets were prepared by direct compression method, compressing the tablet. **Results:** Off all the nine formulations from F1 to F7, F4 show good formulation as the extended layer shows release for about 20 hr and the immediate release layer shows a very good release in 20 mins .

 International Standard Serial Number (ISSN): 2319-8141

INTRODUCTION:

Bilayer tablets: Dual release tablet is a unit compressed tablet dosage form intended for oral application. It contains two layers in which one layer having conventional or immediate release part of single or multiple actives; another layer is sustained or controlled release part of single or multiple actives. They are also called as Bilayer tablet, multi-layer matrix tablet. A bilayer tablet is a type of multiple compressed tablets. Tablets are composed of two layers of granulation compressed together. Monograms and other distinctive marking may be compressed in the surface of the bilayer tablets. Coloring the separate layer provide many possibilities for unique tablets identity.

Applications:

- Bilayer tablets are mainly used in the combination therapy.
- Bilayer tablets are used to deliver the loading dose and sustained dose of the same or different drugs.
- Bilayer tablets are used for bilayer floating tablets in which one layer is floating layer another one is immediate release layer of the drug.
- Bilayer tablets are used to deliver the two different drugs having different release profiles.

Advantages:

- They are used as an extension of a conventional technology.
- Potential use of single entity feed granules.
- Separation of incompatible components.
- Patient compliance is enhanced leading to improved drug regimen efficacy.
- Patient convenience is improved because fewer daily doses are required compared to traditional delivery system.
- Maintain physical and chemical stability.
- Retain potency and ensure dose accuracy.

Disadvantages:

- Adds complexity and bilayer rotary presses are expensive.
- Insufficient hardness, layer separation, reduced yield.
- Inaccurate individual layer weight control.
- Cross contamination between the layers.

BILAYER TECHNOLOGY: Bi-layer tablet is suitable for sequential release of drug in combination, and also for sustained release tablet in which one layer is immediate release as initial dose and second layer is maintenance dose (Shiyani et al., 2008). There is various application of the bi-layer tablet it consist of monolithic partially coated or multilayered matrices. In the case of bi-

layered tablets drug release can be rendered almost unidirectional if the drug can be incorporated in the upper non-adhesive layer its delivery occurs into the whole oral cavity.

VARIOUS TECHNIQUES FOR BILAYER TABLET:

OROS® PUSH PULL TECHNOLOGY: This system consist of mainly two or three layer among which the one or more layer are essential of the drug and other layer are consist of push layer. The drug layer mainly consists of drug along with two or more different agents. So this drug layer comprises of drug which is in poorly soluble form. There is further addition of suspending agent and osmotic agent.

A semi permeable membrane surrounds the tablet core.

L-OROS TM TECHNOLOGY: This system used for the solubility issue Alza developed the L-OROS system where a lipid soft gel Product containing drug in a dissolved state is initially manufactured and then coated with a barrier membrane, than osmotic push layer and than a semi permeable membrane, drilled with an exit orifice

ENSO TROL TECHNOLOGY: Solubility enhancement of an order of magnitude or to create optimized dosage form Shire laboratory use an integrated approach to drug delivery focusing on identification and incorporation of the identified enhancer into controlled release technologies.

DUROS TECHNOLOGY: The system consists from an outer cylindrical titanium alloy reservoir. This reservoir has high impact strength and protects the drug molecules from enzymes. The DUROS technology is the miniature drug dispensing system that opposes like a miniature syringe and reglious minute quantity of concentrated form in continues and consistent from over months or Year.

ELAN DRUG TECHNOLOGIES' DUAL RELEASE DRUG DELIVERY SYSTEM: DUREDAS™ Technology is a bilayer tablet which can provide immediate or sustained release of two drugs or different release rates of the same drug in one dosage form. The tab letting process can provide an immediate release granulate and a modified-release hydrophilic matrix complex as separate layers within the one tablet. The modified-release properties of the dosage form are provided by a combination of hydrophilic polymers. Benefits offered by the DUREDAS™ technology include:

Bilayer tabletting technology.

Tailored release rate of two drug components.

Capability of two different CR formulations combined.

Capability for immediate release and modified release components in one tablet.

Unit dose, tablet presentation.

The DUREDAS™ system can easily be manipulated to allow incorporation of two controlled release formulations in the bi-layer. Two different release rates can be achieved from each side. In this way greater prolongation of sustained release can be

achieved. Typically an immediate release granulate is first compressed followed by the addition of a controlled release element which is compressed onto the initial tablet. This gives the characteristic bi-layer effect to the final dosage form. A further extension of the

BI-LAYER TABLET PRESS: The Bi-Layer Tablet Press features a retractable second layer feeder that permits automated first layer sampling at production speeds. The first layer sampling capability also offers a hardening feature, which the main compression station will automatically compress, the first layer tablet for in-process measurement. The two feeders are zero clearance and are configured with an integrated dust extraction manifold which cleans the die table and completely eliminates any potential for cross contamination. They are available for potent for layer Tablet Press is a small-scale press which is ideal for product development scale-up, clinical trials and midrange production. The bi-layer execution, single-layer conversion kit and exchangeable turret offer unprecedented flexibility.

Ideal properties for bilayer tablets press:

□□Preventing capping and separation of the two individual layers that constitute the bilayer tablet.

□□Preventing cross-contamination between the two layers.

□□Producing a clear visual separation between the two layers.

□□ High yield and accurate and individual weight control of the two layers.

Antibiotic: Antibiotics are drugs used to kill or harm organisms such as bacteria, viruses, funguses and protozoon in living organisms. Antibiotics act via two mechanisms: they kill the microorganisms (bactericide action) and prevent them from reproducing (bacteriostatic action). Antibiotics are among the most frequently prescribed medications in modern medicine. Antibiotics cure disease by killing or injuring bacteria. The first antibiotic was penicillin, discovered accidentally from a mold culture. Antibiotics can help treat infections caused by bacteria but not by viruses. Amoxicillin, an acid stable, semi-synthetic drug belongs to a class of antibiotics called the Penicillins (Beta-lactam antibiotics).

Classification of antibiotic: β-Lactam antibiotics Examples: penicillins (e.g. amoxicillin), Cephalosporins, carbapenems, monobactams, Tetracyclines Example: tetracycline, Macrolide antibiotics Example: erythromycin, Aminoglycosides Examples: Gentamicin, Tobramycin, Amikacin Quinolones Example: Ciprofloxacin (a fluoroquinolone) Cyclic peptides Examples:

Vancomycin, Streptogramins, Polymyxins, Lincosamides Example: clindamycin, Oxazolidinoes, Example: Linezolid (Zyvox), Sulfa antibiotics Example: sulfisoxazole,

MATERIALS: Amoxicillin Trihydrate is a gift samples from Aurobindo Pharma ltd Hyderabad, Crosspovidone, PVP-K30 are from ISP technologies, HPC, EC, HPMC, Methocel are from Colorcon Asia Ltd, MCC from FMC biopolymer, Collidal Silicon dioxide from Degusser, Magnesium sterate from Ferro industry chemicals.

METHODOLOGY: Shift the amoxicillin through 1400 micron mesh. Shift the other materials micro crystalline cellulose, sodium cross providine, hpmc, pvp, ethyl cellulose, methocel, magnesium state, talc through 425 micron mesh (# 40 sieve). Dry the powder at an inlet temperature 50 ± 5 ^{0} C in fluid bed dryer in the range of 11.0 – 13.5 % w/w at 105 ^{0} C auto mode using IR moisture analyser. Mix the amoxicillin tryhydrate and microcrystalline cellulose, crosspovidine, magnesium sterate, talc and blend it for some time in octagonal blender for its proper mixing . This gives blend –A. Mix the amoxicillin tryhydrate and hpmc, pvp, ethyl cellulose, methocel, magnesium sterate, talc and blends it for some time in octagonal blender for its proper mixing. This gives blend –B. Pour the two blends A and B in two hopper of double rotarary press. Compress the blend into bilayer tablet.

Evaluation Tests:

Standard calibration curve of amoxicillin trihydrate in distilled water solution: Solution of aliquots were transferred to 10 ml volumetric flask and diluted upto mark with water solution contain 50, 100, 150, 200, 250, 300, 350 µg/ml of amoxicillin respectively. Then scan was performed at 272nm.

Drug –polymer interaction by fourier-transformation infra red (FTIR) spectroscopy :

The drug polmer and polymer interaction were studied by FTIR spectrometer.

Angle of repose Flow properties of the blend were evaluated by determining the angle of repose and the compressibility index. Tan θ = h/r

Bulk density and Tapped density Both loose bulk density (LBD) and tapped bulk density (TBD) . LBD = weight of the powder / volume of the packing TBD = weight of the powder / tapped volume of the packing

Compressibility index Compressibility index of the powder was determined by Carr's compressibility index as given by : Carr's index (%) = [(TBD – LBD) x 100]/TBD

Hausner ratio It is the ratio of tapped to loose bulk density was calculated by using the following eqn. Hausner ratio = TBD)/ LBD

Evaluation of amoxicillin tablets: Hardness test, Thickness test, Weight variation test, Friability test, Drug content uniformity test, In vitro dissolution studies test, Data analysis.

 International Standard Serial Number (ISSN): 2319-8141

ILLUSTRATIONS

FORMULATION TABLE

EXTENDED RELEASE LAYER

INGREDIANTS	F1	F2	F3	F4	F5	F6	F7
AMOXICILLIN TRIHYDRATE	400	400	400	400	400	400	400
ETHYL CELLOSE	-		75	65	50	-	-
METHOCOL	-	-	25	35	50	-	-
PVP K -30	-	-	-	-	-	20	15
HPMC 4M	50	75	-	-	-	-	-
MCC	150	125	100	100	100	180	185
MAGNESIUM STERATE	5	5	5	5	5	5	5
TALC	5	5	5	5	5	5	5

TABLE NO : 1

IMMEDAITE RELEASE LAYER

INGREDIENT	T1
AMOXICILLIN TRIHYDRATE	250
CROSSPOVIDINE	50
MCC	90
MAGNESIUM STERATE	5
TALC	5

TABLE NO : 2

FIGURE NO: 1

OROS® PUSH PULL TECHNOLOGY

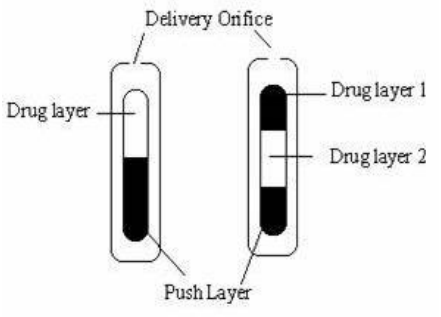

FIGURE NO : 2

L-OROS TM TECHNOLOGY

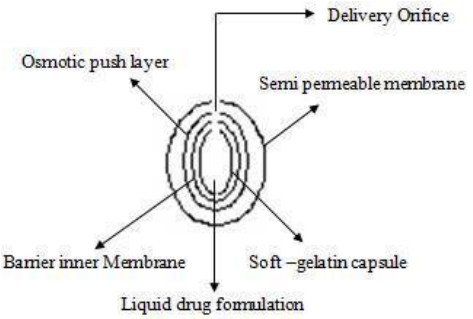

FIGURE NO : 3

DUROS TECHNOLOGY

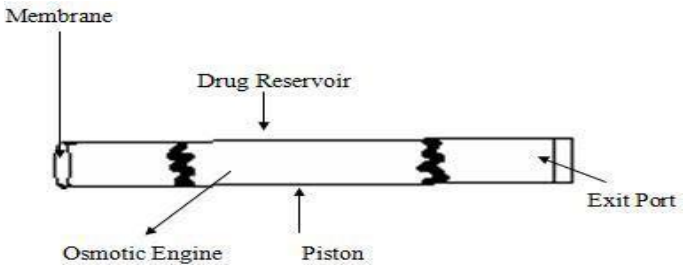

FIGURE NO : 4

 International Standard Serial Number (ISSN): 2319-8141

CALIBRATION CURVE

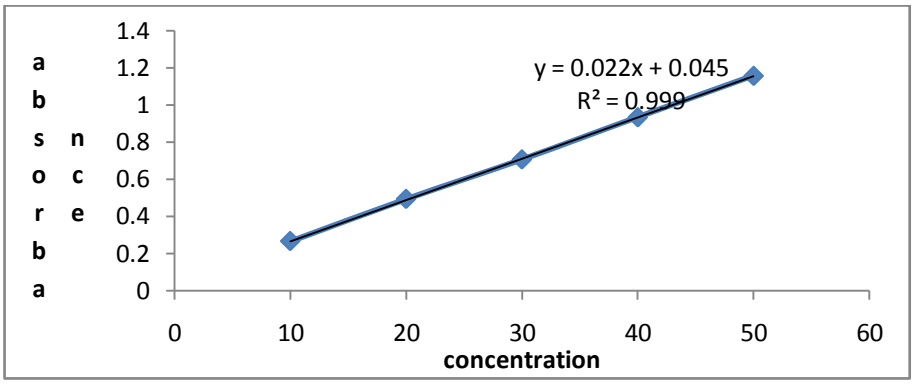

FIGURE NO : 5

Disintegration chart :

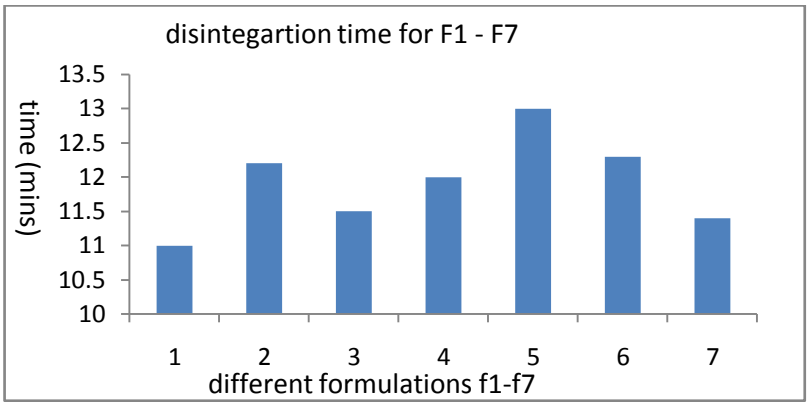

Figure no : 6

Immediate release layer :

Dissolution graph From F1-F7

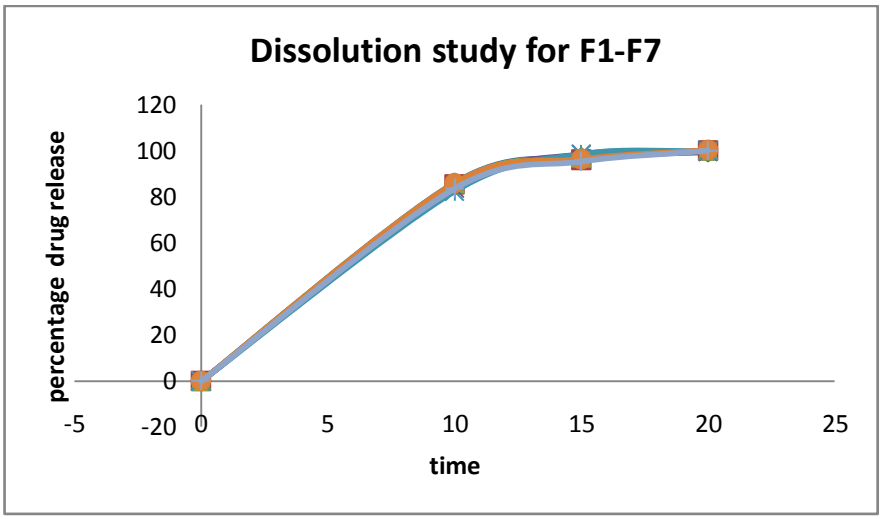

Figure no : 7

Extended release layer from F1 to F7

 International Standard Serial Number (ISSN): 2319-8141

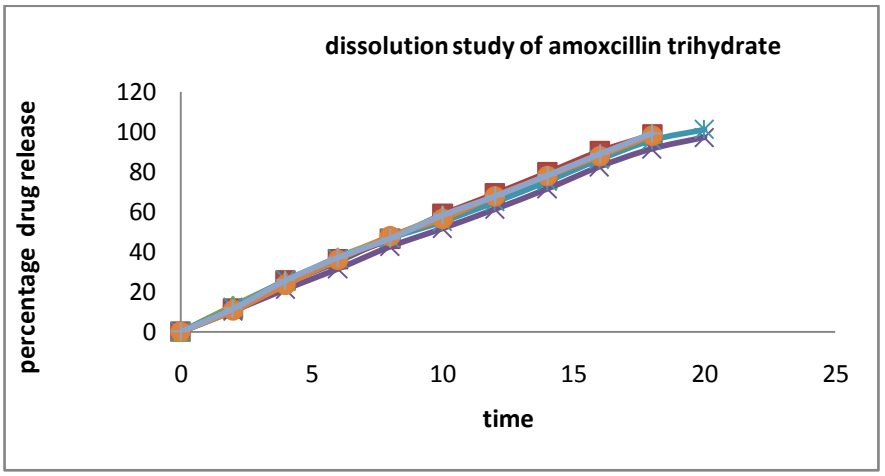

Figure no : 8

Immediate and extended release from f1 to f7

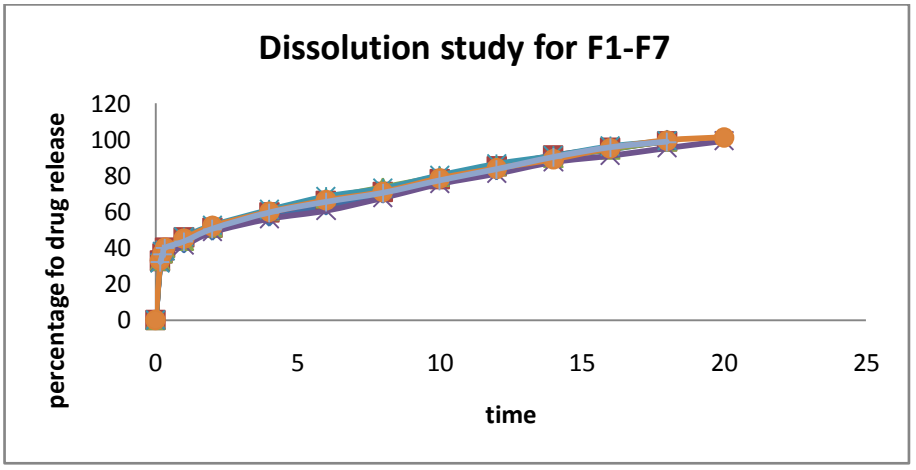

Figure no : 9

RESULTS

Concentration (µg/ml)	**Absorbance**
10	0.267
20	0.494
30	0.707
40	0.934
50	1.157

Table 3: Calibration Curve

PRECOMPRESSION STUDIES :

S.NO	**TEST**	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**
1	**BULK DENSITY(GM/ML)**	0.62	0.61	0.62	0.63	0.61	0.61	0.62
2	**TAPPED DENSITY (GM/ML)**	0.87	0.869	0.87	0.87	0.86	0.87	0.86
3	**CARR INDEX**	28.73	29.06	28.58	29.6	28.73	29.06	07.90
4	**HAUSNERS RATIO**	1.4	1.4	1.38	1.4	1.4	1.4	1.4
5	**ANGLE OF REPOSE**	47.64	48.72	47.61	47.62	47.65	48.01	47.63

Table no : 4

 International Standard Serial Number (ISSN): 2319-8141

POST COMPRESSION STUDY

TEST	F1	F2	F3	F4	F5	F6	F7
AVG.WT	1002	998	995	1004	1001	996	1003
HARDNESS[KG/CM^3]	10.6	10.2	11.1	10.2	10.5	10.4	10.3
FRIABILITY	0.3	0.5	0.1	0.5	0.7	0.1	0.3
LENGTH[MM]	15.1	15.4	15.2	15.2	15.1	15.2	15.1
THICKNESS	6.27	6.24	6.34	6.41	6.19	6.32	6.89
DISINTEGRATION	11mins	12.20	11.50	12	13	12.30	11.40
UNIFORMITY OF WEIGHT	1.72-1.2	1.65-1.30	1.74-1.26	1.50-1.20	1.82-1.20	1.73-1.13	1.75-1.10

Table no : 5

Immediate layer

Test	F1	F2	F3	F4	F6	F7	F8
Disintegration	59 sec	50 sec	1min 20 sec	55 sec	1 min5 sec	1 min 10 sec	58 sec

Table no : 6

Extended release layer

Test	F1	F2	F3	F4	F6	F7	F8
Disintegration	10 mins 30 secs	11 mins	10 mins 15 secs	11 mins 57 sec	11 mins 5 sec	12 min 10 sec	10 mins 58 sec

Table no : 7

Dissolution study: Immediate release layer

Time	F1	F2	F3	F4	F5	F6	F7
0	0	0	0	0	0	0	0
10	86.2	85.4	85.9	83.8	82.4	85.9	83.6
15	97.4	96.2	97.1	98.5	98.5	96.4	95.4
20	99.5	100.2	100.1	99.6	99.9	100.4	100.1

Table no : 8

Dissolution study : Extended release layer:

TIME	F1	F2	F3	F4	F5	F6	F7
2 hr	12.5	11.4	13.1	10.4	12	10.5	11.6
4 hr	24.2	25.5	25.4	21.3	25.8	23.4	25.6
6 hr	35.1	36.2	37.3	31.5	36.5	36	37.1
8 hr	47.2	46.5	47.5	42.6	46.8	47.8	46.7
10 hr	57.1	58.8	58.1	51.7	55.2	56.5	58.3
12 hr	68.9	69.1	67.4	61.3	64.9	67.8	67.8
14 hr	77.3	79.7	76.5	71.5	75.3	77.8	78.2
16 hr	86.5	90.4	87.4	82.6	86.3	87.9	88.9
18 hr	97.4	98.7	98.2	91.5	95.9	98.12	99.2
20 hr	--	--	--	97.2	101.2	-	-

Table no : 9

 International Standard Serial Number (ISSN): 2319-8141

DISSOLUTION STUDY

TIME	F1	F2	F3	F4	F5	F6	F7
10 mins	33.1	32.8	32.9	32.1	31.6	33.0	32.1
15 mins	37.4	37	37.1	37.8	37.8	37	36.6
20 mins	38.2	40	40	38.3	38.4	40	40
60 mins	42.5	45.8	44	41.5	46	45.2	43.5
2 hr	49.5	51	51.4	48.8	52.5	52	50.5
4 hr	57.3	59.5	60.5	56.2	61.1	60	59.5
6hr	63.5	66	67.5	60.7	68.5	66.3	65.4
8 hr	70.1	71	73.5	67.8	73	71	70.4
10 hr	78.2	78	79.5	75.5	80.2	78.5	77.3
12 hr	83	85	85.5	81.2	86.5	84	83.5
14 hr	90.2	91.2	90	87.6	91	89	90.2
16 hr	94.6	95.3	94.6	91.1	96.2	95.2	95.6
18 hr	99.7	98.9	99.1	95.4	99.2	99.5	98.7
20 hr	--	--	--	99.3	--	101.2	--

Table no : 10

DISCUSSION:

In order to achieve the development of combination of immediate and extended release dosage form currently the bilayer technology with multiple layers having a rapid and extended has been investigated. This formulation can be used for treatment for bacterial infections. For the study , amoxicillin trihydrate is used as model drug for treatment of upper respiratory tract infection , tonsilities which is formulated by using direct compression method .

Compatability studies : The IR Spectrum of pure amoxicillin trihydrate and other exipients was compared with the IR spectrum of formulated amoxicillin trihydrate extended release and immediate release of amoxicillin trihydrate tablets. The IR spectrums of the formulation were matching with the IR spectrum of pure amoxicillin trihydrate.

Evaluation of blend: angle of repose for blend is 47.61 – 48 .01 the type flow is poor . to improve flow property magnesium sterate and talc is added to the blend. Bulk density for the granules is : 0.61 – 0.63 gm/ml Tapped density for granules is : 0.86 – 0.87 gm/ml. Carrs index for granules is 27.0 -29.06. Hausner ratio was found to be : 1.38 – 1.4

Evaluation of tablet: All formulations full fill the requirement of uniformity of dosage form. The average percentage of deviation of tablet of each formula is less than ±2. The thickness of all formulation of bilayer tablet is 6.19-6.8 mm. The hardness of all formulation of bilayer tablet is 10.3 – 11.1 kg/cm3. The fraibilty of all batches is less than 1. Dissolution studies for all the formulations from f1 – f8 f4 show good immediate and extended release time.

 International Standard Serial Number (ISSN): 2319-8141

CONCLUSION

Success of the In vitro drug release studies recommends the product for further in vivo studies, which may improve patient compliance. Combination of amoxicillin trihydrate as immediate release layer and amoxicillin trihydrate as extended release layer improves the patient compliance. From the results formulation F-4 has been selected as best formulation among all the other formulations. Formulation F-4 provides better *in vitro* release from layer 1 as well as layer 2.

BIBLIOGRAPHY

1. Tablets: A novel approach to drug delivery:International Journal of Current Pharmaceutical Research 2011 3(1): 1-7.
2. Prakash K,Narayana P, Kumri KS, Narasu ML. Spectrophotometric estimation of amoxicillin Trihydrate in bulk and pharmaceutical dosage form.E-Journal of chemistry,2008;5(S2):1114-1116.
3. Lachman L, Lieberman HA, L. Kanig JL.The theory and practice of industrial pharmacy. 3rd edition, Varghese Publishing House, 1990: 317
4. Raymond C Rowe Hand book of Excipients 5th ed. 2006;Sodium starch glycolate: 701- 704.
5. New york 2005; Tablet vol I & II , 2nd edition revised and expanded: Pg no 106-600.
6. Indian pharmacopoeia, Vol I & II, 1996, Controller publications, New Delhi, p.no.172.
7. British pharmacopoeia, Vol I, 2007, The stationary office on behalf of the medlines and health care productsregulatory agency(MHRA),London.
8. National formulary of India,3rd edition, controller publication pg no 254-323.
9. Dr. Ali R Rajabi-Siahboomi, "An Over view of Current Oral Modified Release Technologies", Drug Delivery Oral, business briefing: pharmatech, 2003, pp. 181-184.
10. Syed azeem, Shawetasharma, "Immediate Release Drug Delivery Systems: A Review", International Journal of Biopharmaceutical & Toxicological Research, May 2011, pp. 24-25.
11. Madhusudhanpogula, S. Nazeer, "Extended Release Formulation", International Journal of Pharmacy & Technology, Dec-2010, 2, pp. 625-84.
12. Araya Raiwa, , "Formulation Development Strategies For Oral Extended Release Dosage Forms", Bangkok, Thailand, May, 2011.
13. Formulation, solid dosage form-tablet formulation.vinensia.com/2011/02/tablet-solid-dosage-form.html
14. K.Senthil Kumar, M.pharm thesis, "pharmaceutical technology-II, tablet", QIS college of pharmacy- Ongole A.P, India.

 International Standard Serial Number (ISSN): 2319-8141

15. Formulation, solid dosage form-capsule formulation.vinensia.com/2011/04/capsule-solid-dosage-form.html

16. Prof. James a. Syce, m.pharm thesis, "The formulation, manufacture and evaluation of capsules containing freeze-dried aqueous extracts of leonotisleonorusor menthalongifolia", University of the Western Cape, South africa, June 2006.

medicalnewstoday.com/articles/10278.php Antibiotic review, April 2004.

17. "Guidance for Industry Streptococcal Pharyngitis and Tonsillitis - Developing Antimicrobial Drugs for Treatment", july-1998.