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Formulation & Evaluation Immediate Release of Clarithromycin by Using k-30 Disintegrate

K. Tejaswi[1], P.V.Rao[2], P. Sowmya[3], Sk. Karishma[3], Sk. Nagulmeera[3], Sk. Reshma[3].

St. Mary's College of Pharmacy, St. Mary's Group of Institutions Guntur, Chebrolu (V&M), Guntur (Dt) Andhra Pradesh -522212

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Corresponding author: K. Tejaswi

Abstract

Based on solubility data 0.1 N HCL was selected as the dissolutionmedium.Bulk density was found to be 0.321 g/ml and CI was 55.07 % indicating that drug has to be granulated for the good flowproperties.Melting point was found to be 257 ^{0} C indicating that drug has less sensitivity for drying temperatures.Drug – excipient compatibility studies indicate that all excipients used in the formulation are compatible with the drug. RS(relatedsubstances) was found to be less than 0.5%. Among the 12 formulations prepared, formulation F12 was found to exhibit all the required properties. This is found to be pharmaceutically stable, once a day, robust formulation.The physical attributes of the tablet were found to be satisfactory.Typical tablet defects such as capping, chipping and picking were not observed.Thetotalweightofeachformulationwasmaintainedconstantandtheweightvariation of the tablets was within limits of5%.Hardness was found to be 8.6KPFriability was calculated as 0.15% which was within the acceptable range of 1% and indicated that tablet surfaces are strong enough to withstand mechanical shock or attrition during storage andtransportation.Assay values were found to be within acceptablelimits.The stability study for the selected formulation F12 was performed as per ICH guidelines. Stability study was carried out for 2 months at 40° C, 75% RH, according to ICH guidelines. The tablets were tested for drug release during the stability period and confirmed that results were found within thelimits. The stability data reveals tha tthe F12 showed an egligible changein drug content after storage in various conditions for two months according to ICHguidelines.

Keywords: Clarithromycin, ICH guidelines.

Introduction

ORAL DRUG DELIVERY

Oral drug delivery is the most widely utilized route of administration among all the routes of administration that has been explored for the systematic delivery of drug through different pharmaceutical dosage forms. The popularity, of oral drug delivery may be in partly attributed to its ease of administration as well as the traditional belief that by oral administration, the drug is well absorbed because of the food stuff that are ingested daily. In fact, the development of a pharmaceutical product for oral delivery, irrespective of its physical form(solid, semisolid, or liquid dosage forms), involves various extents of optimization of dosage form characteristics within the inherent consistent of gastrointestinal physiology [1].

The oral route of drug administration is the most important method of drugs for systemic affects. It can be said that at least 90% of all drugs used to produce systemic effect by are administered orally. They present wide range of comforts to manufacturer as well as the patient [2].

A drug delivery system (DDS) is defined as a formulation or a device that enables the introduction of a therapeutic substance

into the body and improves its efficacy and safety by controlling the rate, time, and site of release of drugs in the body. The goal of any drug delivery system is to provide a therapeutic amount of drug in the proper site in the body to achieve promptly and then to maintain the desired drug concentration. Oral route of drug administration is most appealing route for delivery of drugs for various dosage forms [3,4,5].

The first step in the development of dosage form is Preformulation, which can be defined as investigation ofphysiochemicalpropertiesofdrugsubstancesaloneandwhencombinedwithexcipients.Themainobjective of Preformulation studies, is to develop stable and bioavailable dosage form and study of factors affecting such as stability, bioavailability and to optimize so as to formulate the best dosage form. Here, optimization of formulation means finding the best possiblecomposition [4].

Compressedtabletsareformedbyapplyingpressure,forwhichcompressionmachines(tabletpresses)are used and they are made from powdered crystalline or granular material, alone or in combination with binder, disintegrants, release polymers, lubricants and diluents and in some cases withcolorant.

Tablets [5,7]

Tablets may be defined as the solid pharmaceutical dosage forms containing drug substances with or withoutsuitablediluentsandpreparedeitherbycompressionormouldingmethods.Theyhavebeeninwidespread use since the latter part of the 19th century and their popularity continues. The term compressed tabletisbelieved to have been first used by "JOHN WYETH". Tablets remain popular as a dosage form because of the advantages afforded both to the manufacturer and the patient.

Properties of tablets [5,7]

The attributes of an acceptable tablet are as follows:

The tablet must be sufficiently strong and resistant to shock, abrasion, should withstand handlingduring manufacturing, packing, shipping, and use. Hardness and friability tests measure thisproperty.

Tablet must be uniform in weight and in drug content of the individual tablet.This is measured by the weight variation and content uniformitytests.

Thedrugcontentofthetabletmustbebioavailable.This propertyismeasuredbythedissolution test. Accurate bioavailability can be obtained from the drug levels in the blood after itsadministration. Tablets must retain all these functional attributes which include drug stability andefficacy.

Advantages ofTablets

They are unit dosage forms, so they offer greater capabilities of all oral dosage forms for thegreatest dose precision and the least contentvariability.

They are easy toadminister.

Large scale manufacturing is feasible in comparison to other dosage forms. Therefore economycan beachieved.

Accuracy of dose is maintained since tablet is a solid unit dosageform.

Longer expiry period and minimum microbial spillage owing to lower moisturecontent.

As tablet is not a sterile dosage form, stringent environmental conditions are not required inthe manufacturing department.

Ease of packaging (Blister or Strip) and ease of handling over liquid dosageforms.

In comparison to capsules, tablets are more tamperproof[8].

Disadvantages oftablets:

Some drugs resist compression into dense compacts, owing to their amorphous nature orflocculent, low densitycharacter.

Drugs with poor wetting, slow dissolution properties, intermediate to large dosages,

andoptimum absorption in the gastrointestinal tract or any combination of these features may be difficultorimpossible to formulate and manufacture as a tablet that will still provide adequate of full bioavailability.

Bittertastingdrugs,drugswithobjectionableodourord rugsthataresensitivetooxygenoratmospheric moisturemayrequireencapsulationoraspecialtypeofc oatingwhichmayincreasethecostoffinished product.

Some drugs may be unsuitable for administration by oralroute.

Difficult to swallow for kids, terminally ill and geriatricpatients [9].

Types oftablets

Tablets are classified as follows:

According to the drug release rate from thetablet.

According to the method of manufacturing.

According to the route of administration orfunction [10].

According to the drug release rate from the tablet (USPclassification)

Immediate release or conventional tablets

The tablet is intended to be released rapidly after administration or the tablet is dissolved and administered as a solution. It is the most common type and it includes.

Disintegratingtablet

Chewabletablet

Sublingualtablet

Buccaltablet

Effervescenttablet

Modified release tablets

They have release features based on time, course or location. They mustbe swallowedintact.

Delayed release tablets – Drug release is delayed due to physiological conditions.

Extended release tablet – Allows the reduction in dosingfrequency[11,12].

According to the method of manufacturing [7,8]:

Compressed tablet

It is obtained by compressing uniform volume of particles using"Tablet compression machine". It is used for large scale production. E.g. Paracetamoltablet.

Moulded tablet

Moulding means shaping, hardening of semisolid mixture of drug and excipients. It is obtained by "tablet mould". It is restricted to small dose tablet and small scale production. E.g. Nitro-glycerineTablet.

Molded tablets or tablettriturates:

Dispersingtablets

Hypodermictablet

Immediate release drug deliverysystem

Immediate release drug delivery system is also conventional type of drug delivery system as it is defined as – Immediate release tablets are designed to disintegrate and release their medicaments with no special rate controlling features such as special coatings and other techniques[13].

Advantages of immediate release drug deliverysystems**:**

Release the drugimmediately.

More flexibility for adjusting thedose.

It can be prepared with minimum dose ofdrug.

There is no dose dumpingproblem.

Immediate release drug delivery systems used in both initial stage and final stage ofdisease.

At the particular site of action the drug is released from thesystem.

Tablet Excipients [7]

An excipient is generally a pharmacologically inactive substance used as a carrier for the active ingredients of a medication.Inmanycases,an"active"substance(sucha sacetylsalicylicacid)maynotbeeasilyadministeredan d absorbed by the human body; in such cases the substance in question may be dissolved into or mixed with an excipient[14,15].

ROLE OF CLARITHROMYCIN

Immediate release drug delivery system based on single or multiple unit reservoir or matrix system, whicharedesignedtoprovideoftime.

Immediatereleasedrugdeliveryisdesirablefordrugsh aving long biological half-life high bioavailability. Oral drug delivery is the most desirable and preferred method administering therapeutics agent for their systematic effect. In addition, the oral medication is generally considered as the first avenue investigated in the discovery and development of new entities and pharmaceutical formulation, mainly because of patient acceptance, convenience in administration and cost effective manufacturingprocess.

Clarithromycin is a macrolide antibiotic with broad spectrum of activity. It is given the treatment of respiratory tract infection in the skin and soft tissue infection. Clarithromycin may be given to eradicate H. pylori in treatment regimens for peptic ulcer

diseases. Clarithromycin has *nvitro*antibacterial activity against typical (streptococcus, pneumonia, influenza, Moraxella) atypical (mycoplasma pneumonia, chlamydia pneumonia, legionella) pathogens commonly associated acquired lower respiratory tract infections. Clarithromycin is rapidly absorbed from the GIT and undergoesfirstpassmetabolism.Thebioavailabilityof thedrugisabout55%.Theterminalhalf-life ofclarithromycinisreportedlyabout 3-4 hrs. Comparedwitherythromycin,clarithromycinpossesses greater acid stability, improved pharmacokinetic properties and fewer GIT, rapid gastrointestinal absorption,highlysolubleatacidicpHabsorptionofclarithromycinisunaffectedbyfood.Morethan half of an oral dose is systematically available as the parent drug and the active 14- hydroxyl metabolite, pharmacokinetics or nonlinear, with plasma concentration increasing in more than proportion to the dosage. First pass metabolism results in the rapid appearance of the active metabolite.

MATERIALS AND METHODS

S.No.	Name of the material	Category	Supplier
1	Clarithromycin	Active Pharmaceutical Ingredient	Aurobindo Pharma Limited
2	Lactose monohydrate	Diluent	FMC biopolymer
3	Micro Crystalline Cellulose(Avicel pH 101)	Diluent	FMC biopolymer
4	Sodium Starch Glycollate	Disintegrant	SD Fine, Mumbai
5	Povidone k-30	Binder	BASF, Germany
6	Micro Crystalline Cellulose(Avicel pH 102)	Diluent	FMC biopolymer
7	Light anhydrous silicic acid (Aerosil 200	Glidant	Evonik Degussa
	pharma)		GmBH, Germany
8	Magnesium Stearate	Lubricant	Kawarlal Excipients limited

METHOD OF ESTIMATION OF CLARITHROMYCIN:

ANALYTICAL METHODS:

ESTIMATION OF CLARITHROMYCIN

A Spectrophotometric method based on the measurementofabsorbanceat235nmin0.1NHClwasusedinthepresentstudyfortheestimation ofClarithromycin.

REAGENTS

Preparation of 0.1N HCl

8.5ml of concentrated HCl was taken in a volumetric flask and it was made up to 000ml with distilled water.

STANDARD SOLUTION

100 mg of Clarithromycin pure drug was dissolved in 100 ml of 0.1 N HCl (stock solution- 1000 µg/ml), from this 10 ml of solution was taken and the volume was adjusted to 100 ml with 1N HCl (100µg/ml) [16].

PROCEDURE

The above solution was subsequently diluted with 0.1N HCl to obtain the series of dilutions containing 2,4,6,8,10,12,16,20,24,30, and 100µg/ml ofClarithromycin.

The absorbance of the above dilutions was measured at 235 nm by using the UV-Spectrophotometer using 0.1N HCl as theblank. Then a graph was plotted by taking Concentration on X-Axis and Absorbance on Y- Axis which gives a straightline.

FORMULATION DEVELOPMENT OF CLARITHROMYCIN IMMEDIATE RELEASE TABLETS

From the powder flow characteristics and BD (Preformulation Studies) of Clarithromycin API, it was found to be not suitable for direct compression. It was decided to formulate the tablet by wet granulation process.

The following formulations are prepared by maintaining the effective processing conditions, NMT 50% RH and NMT 60 ºC temperature.

The method used in making these tablets is as follows

STEP 1. WEIGHING

RequiredquantitiesofClarithromycin,diluents,andotherexcipientsasgiveninthetablewere weighedseparately [19].

STEP 2. CO MILLING

Clarithromycin, Lactose monohydrate and light anhydrous silicic acid were co-milled through 0.991mm screen at medium speed [20].

STEP 3. SIFTING

Micro crystalline cellulose and Sodium starch glycollate were co sifted along with above step through #30mesh [21].

STEP 3. GRANULATION

Granulation was done in Rapid Mixer Granulator using binder solution (Povidone in purified water).The above step materials were loaded into RMG [22].

The granulation parameters are as follows

STEP 4. DRYING

The granules were dried in rapid drier at 60 ° C to obtain an LOD of NMT 3% w/w.

STEP 5. SIZING OF GRANULES & BLENDING

The dried granules are passed through #25 mesh and the retains were milled through Co mill 0.991mm screen at medium speed [23].

STEP6. PRE LUBRICATION

The materials of above step were loaded into a suitable blender and blended for 10 minutes.

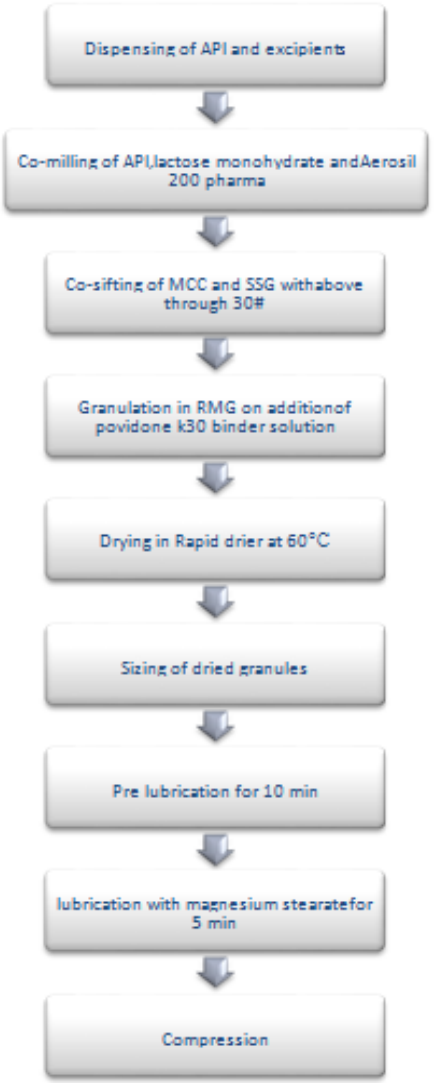
STEP 7. LUBRICATION

Required concentration of magnesium stearate was weighed, passed through #60 mesh and blended with blend from step 5 for 5 min 24.

STEP 8. COMPRESSION

The granules obtained were compressed with 9.5 × 4.6 (for 75 mg strength), 9.0 × 4.0 (for 50 mgstrength)and 8.0×3.1(for 25 mg strength) round shaped, deep concavepunches with break line on oneside [17,18].

FLOW CHART FOR FORMULATION OF CLARITHROMYCIN TABLETS



Composition of Clarithromycin Immediate Release Tablets (F1-F6)

S.NO	INGREDIENTS	F1	F2	F3	F4	F5	F6
A.Drymix		Quantity(mg/tab)					
1.	Clarithromycin	75.00	75.00	75.00	75.00	75.00	75.00
2.	Lactose monohydrate	130.20	180.00	195.00	189.00	195.00	175.00
3.	Microcrystalline Cellulose 101	55.80	-	-	-	-	-
4.	Aerosil 200 pharma	-	-	-	-	-	-
5.	Sodium Starch Glycollate	6.00	6.00	6.00	6.00	6.00	6.00
B.BINDER SOLUTION							
5.	Povidone K30	9.00	9.00	9.00	15.00	9.00	6.00
6.	Purified Water	q.s	q.s	q.s	q.s	q.s	q.s
C. BLENDING							
7.	Microcrystalline Cellulose 102	15.00	21.00	6.00	6.00	6.00	30.00
8.	Sodium Starch Glycollate	6.00	6.00	6.00	6.00	6.00	3.50

9.	Aerosil 200 pharma	1.50	1.50	1.50	1.50	1.50	3.00
D. LUBRICATION							
10.	Magnesium stearate	1.50	1.50	1.50	1.50	1.50	1.50

S.NO	INGREDIENTS	F7	F8	F9	F10	F11	F12
A.Drymix		**Quantity (mg/tab)**					
1.	**Clarithromycin**	75.00	75.00	75.00	75.00	75.00	75.00
2.	**Lactose monohydrate**	175.00	175.00	189.00	150.00	150.00	150.00
3.	**Microcrystalline Cellulose 101**	-	-	-	45.00	45.00	45.00
4.	**Aerosil 200 pharma**	1.50	3.00	-	6.00	6.00	6.00
5.	**Sodium Starch Glycollate**	6.00	6.00	6.00	12.00	12.00	12.00
B.BINDER SOLUTION							
5.	**Povidone K30**	**6.00**	**6.00**	**15.00**	**9.00**	**9.00**	**9.00**
6.	**Purified Water**	**q.s**	**q.s**	**q.s**	**q.s**	**q.s**	**q.s**
C. BLENDING							
7.	**Microcrystalline Cellulose 102**	30.00	30.00	6.00	-	-	-
8.	**Sodium Starch Glycollate**	3.50	3.50	6.00	-	-	-
9.	**Aerosil 200 pharma**	1.50	1.50	1.50	-	-	-
D. LUBRICATION							
10.	**Magnesium stearate**	1.50	1.50	1.50	3.00	3.00	3.00
Average weight (mg)		300.00	300.00	300.00	300.00	300.00	300.00

Average weight (mg)	300.00	300.00	300.00	300.00	300.00	300.00

Composition of Clarithromycin Immediate Release Tablets (F7-F12)

RESULTS ANDDISCUSSIONS

The present study was undertaken to formulate Clarithromycin immediate release tablets. The study involves pre formulation studies of drug and excipients, formulation and processing development along with evaluation of tablet s made with the optimized formulation. Finally, the tablets were evaluated by *invitro*methods. Results and discussion of the above studies are presented below:

Particle Size Distribution (PSD)

Particle size distribution of Clarithromycin

Sieve no	Empty sieve(gm)	Sample sieve(gm)	Difference (gm)	%Retained	%Cumulative Retained
#20	321.4	321.4	0	0	0
#30	328.6	328.8	0.2	0.2	0.2
#40	299.0	300.0	1.0	1.0	1.2
#60	287.2	297.4	10.2	10.2	11.4
#100	255.0	275.0	20.0	20.0	31.4
#120	274.0	299.0	25.0	25.0	56.4
#200	270.0	303.2	33.2	33.2	89.6
Receiver	348.8	359.0	10.2	10.2	99.8

Weight of sample=100 gm

Through this sieve analysis we came to know that as large quantity of powder was retained on sieve no. 200, the flow property of the drug was determined to be poor. Flow property and particle size are inversely proportional to each other as Clarithromycin has fine grade of particles, it has poorflow.

DRUG EXCIPIENTS COMPATIBILITY STUDY

S. No	Name of the Excipient	Ratio API: Expt	Initial Observation	Final observation 40°C/75% RH		Conclusion
				2nd week	4th week	
1	API (Clarithromycin)	---	Off-White	Off- White	Off- White	Compatible
2	API+ Lactose monohydrate	1 :1	Off-White	Off- White	Off- White	Compatible
3	API + MCC 101	1 : 1	Off-White	Off- White	Off- White	Compatible
4	API + Sodium starch glycollate	1 : 1	Off-White	Off- White	Off- White	Compatible
5	API +Aerosil 200 pharma	1 : 1	Off-White	Off- White	Off- White	Compatible
6	API + Povidone	1 : 1	Off-White	Off- White	Off- White	Compatible
7	API +MCC 102	1 : 1	Off-White	Off- White	Off- White	Compatible
8	API + Magnesium stearate	1 : 1	Off-White	Off- White	Off- White	Compatible

FORMULATION DEVELOPMENT

Clarithromycin immediatereleasetabletswere prepared and evaluated. In the present study 12 formulations were prepared and evaluated for physico-chemical parameters, quality control tests and stabilitystudies.

BLEND PROPERTIES OF DIFFERENT FORMULATIONS

Flow properties of blends of various trial batches

Formulation	Blend Property				
	B.D (gm/ml)	T.D (gm/ml)	C.I (%)	H.R	Angle of Repose
F1	0.49±0.013	0.62±0.061	20.97±2.445	1.26±0.028	44.91±2.05
F2	0.613±0.008	0.795±0.025	22.95±0.009	1.298±0.009	26.52±1.32
F3	0.66±0.003	0.75±0.165	9.56±0.009	1.18±0.165	29.56±1.64
F4	0.78±0.012	0.86±0.231	9.36±0.156	1.14±0.156	27.46±1.52
F5	0.72±0.011	0.79±0.013	9.24±1.447	1.10±0.018	28.41±1.69
F6	0.62±0.028	0.69±0.009	7.91±0.124	1.08±0.015	29.25±1.39
F7	0.68±0.009	0.74±0.011	8.20±0.098	1.89±0.001	28.54±0.42
F8	0.70±0.089	0.77±0.011	8.29±0.089	1.09±0.021	29.96±2.18
F9	0.62±0.015	0.67± 0.006	7.60±0.075	1.08±0.005	29.93±1.70
F10	0.544±0.014	0.697±0.018	22±0.224	1.282±0.011	28.47±0.70
F11	0.58±0.012	0.76±0.231	8.36±0.156	1.24±0.156	24.46±1.52
F12	0.584±0.015	0.735±0.05	20.513±0.226	1.258±0.014	26±0.014

Physical Evaluation of tablets of various trial batches

S. No	Physical parameter	F 1	F 2	F 3	F 4	F 5	F 6	F 7	F 8	F 9	F 10	F 11	F 12
1	Weight variation	1.65	1.57	1.42	1.54	1.18	1.35	1.44	1.23	1.48	1.54	1.63	1.38
2	Hardness (KP)	8.8	8.4	8.2	9.4	9.1	8.8	9.4	8.8	8.5	8.8	9.0	8.6
3	Thickness (mm)	4.41	4.40	4.50	4.37	4.37	4.85	4.89	4.90	4.93	4.12	4.02	4.14
4	Friability %	0.05	0.12	0.10	0.18	0.12	0.07	0.06	0.14	0.15	0.18	0.10	0.15
5	Disintegration time	3min 25sec	2min 30sec	2min 24sec	1min 29sec	1min 45sec	1min 20sec	1min 30sec	1min 40sec	1min 20sec	1min 18sec	1min 10sec	1min 10sec

Chemical evaluation of tablets of various trial batches

S No	Parameter	F 1	F 2	F 3	F 4	F 5	F 6	F7	F8	F9	F10	F 11	F12
1	Assay (%)	99.9	98.6	98.5	100.7	98.7	99.5	98.7	99.6	100.6	98.7	98.9	98.7
2	Dissolution study (NLT 75% in 45 mins)	63.9	62.4	59.6	63.6	60.0	72.8	58.7	67.4	65.7	85.5	75.7	86.7

DISSOLUTION STUDIES

The dissolution was carried out for different experimental trials. The various results that are obtained are tabulated below. Dissolution studies are carried out in the following media.

Medium : 0.1NHCL

Typeofapparatus :

USP - II (paddle type) RPM : 50rpm

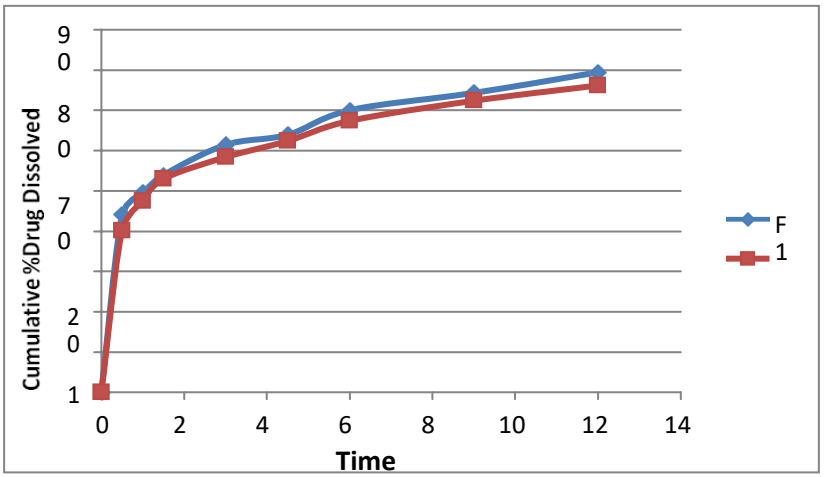
Volume : 900 ml

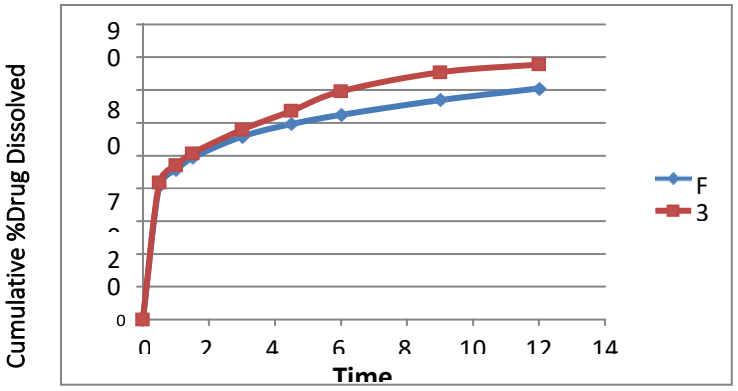
Temperature : 37ºC±0.5ºC

Time :2hrs

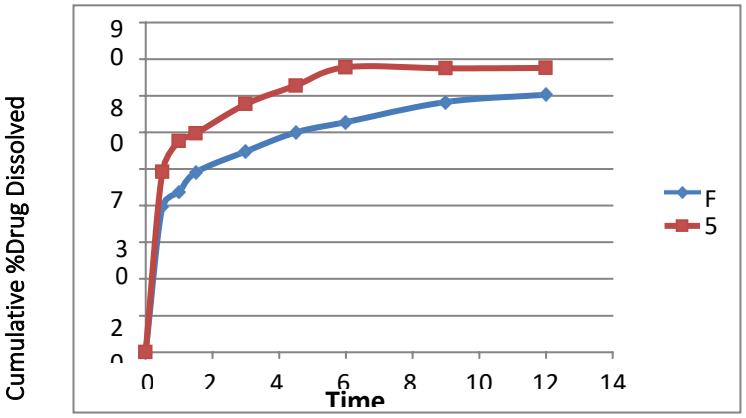
DISSOLUTION PROFILES

Dissolution profile of Clarithromycin Immediate Release tablets (F1, F2)

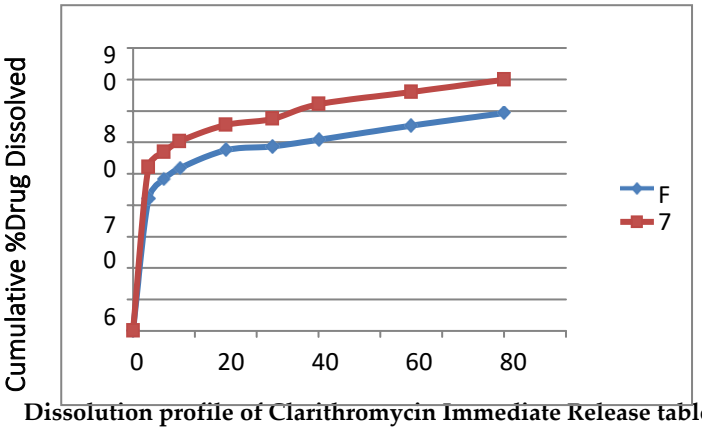




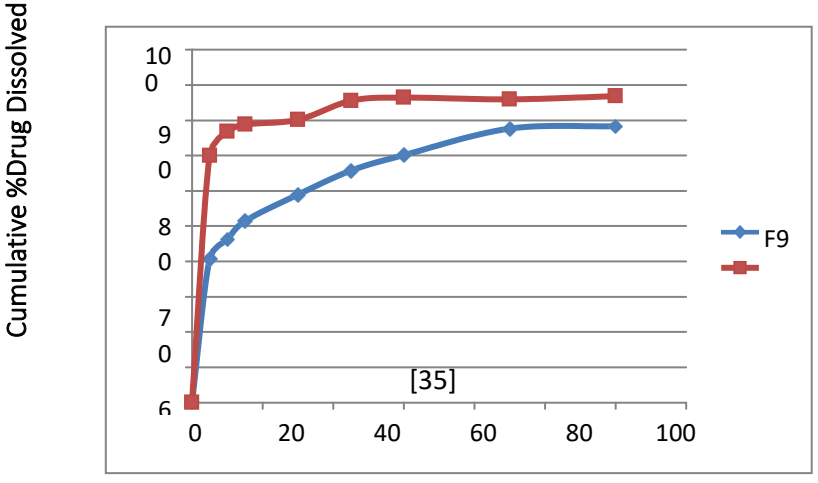
Dissolution profile of Clarithromycin Immediate Release tablets (F3, F4)



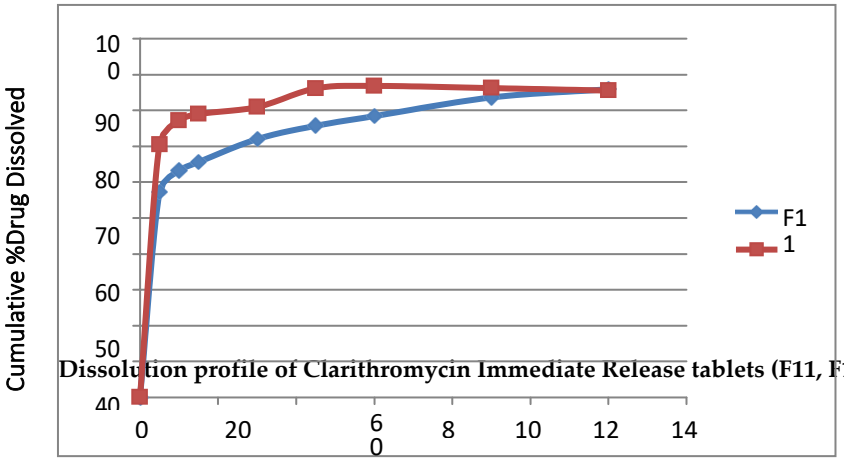
Dissolution profile of Clarithromycin Immediate Release tablets (F5, F6)



Dissolution profile of Clarithromycin Immediate Release tablets (F7, F8)



Dissolution profile of Clarithromycin Immediate Release tablets (F9, F10)



Dissolution profile of Clarithromycin Immediate Release tablets (F11, F12)

SUMMARY ANDCONCLUSION

This dissertation work was done with an aim to design an immediate release oral dosage form of Clarithromycin and evaluation of the tablets including *in vitro* drug release studies.Clarithromycin immediate release tablets were formulated by using microcrystalline cellulose (diluent), Sodium starch glycollate (super disintegrant), Povidone K 30 (binder) and magnesium stearate (lubricant) and Aerosil 200 pharma (carrier/glidant).The granules were compressed into tablets and were analyzed for the parameters such as average weight, disintegrationtime,friability, thickness, weightvariation,hardnessanddrug content.The formulation F12 showed improved disintegration time when compared to Brand product.ThedissolutionprofileoftheformulationF12 wasfoundtohaveequivalentpercentage drug release with that of the innovator product(f_2=70.65)No significant change was observed in the drug content, physical properties and dissolution rate of these tablets after the storage period of 2 months at 40° C and 75% RH.The formulation F12 and process can be easily scaled up and can be easily employed in large scale production because the process is simple, cost effective, and pharmaceutically stable and also yields reproducible good tablets.

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