FORMULATION & EVALUATION OF ROXITHROMYCIN TABLET FOR RESPIRATORY TRACT INFECTION

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ABSTRACT

The aim of this study was to develop microspheres based orodispersible tablets of roxithromycin using the solvent evaporation technique. The microspheres were formulated in to orodispersible tablets using direct compression technique by central composite design. The objective of the study was to analyze the effect of concentration of eudragit RS100 (F_1) and concentration of polyvinyl alcohol (F_2), on the entrapment efficiency of the drug. Tablets were evaluated for physical characteristics viz. weight variation, hardness, friability, disintegration time and in-vitro dissolution study. The hardness and weight variation of the tablet were found 5.17 ± 0.76 kg/cm and 644.6 ± 6.3 mg, respectively. Friability of tablets was found 0.74 which is less than 1% or in the acceptable limit. Thikness of tablet were found 6.30 ± 0.10 mm. The drug release data were subjected to drug release kinetics study.

Keywords: Dual release system, Dual drug delivery system, Roxithromycin, Factorial design, HPMC K4M, HPMC K15M, Floating lag time.

1.INTRODUCTION

- **Upper Respiratory Tract Infection**

Upper respiratory tract infections (URTI) are the illnesses caused by an acute infection which involves the upper respiratory tract: nose, sinuses, pharynx or larynx. This commonly includes tonsillitis, pharyngitis, laryngitis, sinusitis, otitis media, and the common cold.

The respiratory tract is the most common site of infection by pathogens. The respiratory tract is a frequent site of infection because it comes in direct contact with the physical environment and is exposed to airborne microorganisms. A wide range of organisms can infect the respiratory tract, including viruses, bacteria, fungi, and parasites (Table 1.1).

Table 1.1 Common Causes of Various Upper Respiratory Tract Diseases by Location

Disease Location	Disease	Group of Pathogen	Comments
Nasal passages	Common cold	Viruses	Most common cause rhinovirus

Nasal sinuses	Rhinosinusitis	Viruses Bacteria	Viruses are the most common cause of rhinosinusitis
Pharynx	Pharyngitis	Viruses *Streptococcus pyogenes* and *Corynebacterium diphtheriae*	Viruses cause 90% of these infections

The anatomy of the upper respiratory tract contains several structures that help rid the system of particles and pathogens. The nasal cavity has a mucociliary lining similar to that of the lower respiratory tract. The inside of the nose is lined with hairs, which act to filter larger particles that are inhaled. The turbinate bones are covered with mucus that collects particles not filtered by nasal hairs. The baffle plates cause the air as it passes to swirl forcing the particles to make contact with the mucus covering the nasal passages. Usually, particles 5–10 μm in diameter are either trapped by nasal hairs or impinge on the nasal mucosal surfaces.

Most of the surfaces of the upper respiratory tract (including nasal and oral passages, nasopharynx, oropharynx, and trachea) are colonized by normal flora, which is regular inhabitants and rarely causes disease. The normal flora of the upper respiratory tract has two main functions that are important in maintaining the healthy state of the host: These organisms compete with pathogenic organisms for potential attachment sites, and they can produce substances that are bactericidal and prevent infection by pathogens.

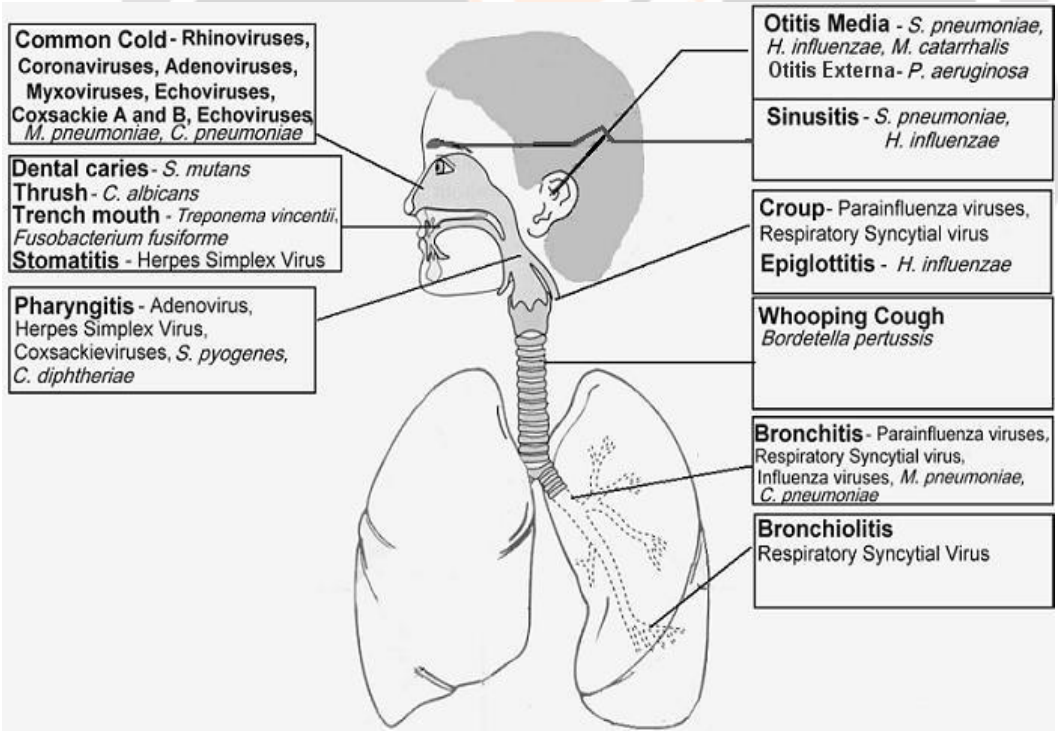


Figure 1.1 Classification of Respiratory Disease

- **Treatment of Upper Respiratory Tract Infection**

Antimicrobial agents, analgesics, antipyretics, and mucolytics are used for the treatment of various upper respiratory tract infections. Antimicrobials are administered to eradicate the pathogen(s), prevent recurrences and complications

and to facilitate recovery. Therapy includes antimicrobial agents amongst macrolides, penicillin, cephalosporin, beta-lactamase inhibitor, etc. the macrolides are the right choice in the treatment of such type of infections.

- **Dual Drug Delivery System**

Dual drug delivery systems are designed to release a drug at 2 different rates or in 2 different periods of time. A quick/slow release system provides an initial burst of drug release followed by a constant rate (ideally) of release over a defined period of time. This type of system is used primarily when maximum relief needs to be achieved quickly, and it is followed by a sustained release phase to avoid repeated administration. Suitable candidate drugs for this type of administration include NSAIDs and antihypertensive, anti-diabetic, antihistaminic, and anti-allergic agents. Generally, conventional controlled dosage forms delay the release of therapeutic systemic levels and do not provide a rapid onset of action. To modify the release of the drug from these systems, the surface area exposed to a fluid can be restricted by the addition of barrier layers to one or both sides of the tablets. When a single constant rate for drug release does not entirely satisfy the therapeutic objective, the quick/slow delivery system may be an interesting alternative. This biphasic release system can be achieved by the application of an immediate release coat portion to the conventional tablet. Another approach to achieve quick/slow drug release involves the use of a compressed core. The core consists of a sustained release tablet, which is coated by compression over the whole surface with a fast-disintegrating formulation. Both the core tablet and the outer powder layer contain a drug. From the viewpoint of manufacturing, this technology is an attractive alternative to the production of multilayer dosage forms, because getting additional layers to adhere to the pre-compressed layers during the double-layer or multilayer tableting process can be difficult. Furthermore, because this system uses conventional manufacturing methods, it is more acceptable to the industry. The proper combination of the quick and sustained release phases would allow the optimization of the fast- and slow-dose fractions as a function of the drug pharmacokinetics and metabolism.

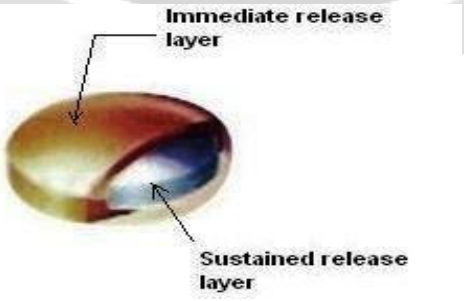
- **Types of Dual Release System**

- **Core Compressed Matrix Tablet:**

This tablet contains a tablet within the tablet. One inner tablet is the core tablet and the drug release is slowly from it. The outer tablet is coat tablet and drug release from this site is fast. Formulation of a core tablet requires two granulations. The core granulation is usually compressed lightly to form a loose core & then transferred to a second die cavity where a second granulation containing additional ingredients is compressed further to form the final tablet (Figure 1.2).

Figure 1.2 Image of Core Compressed Matrix Tablet

Generally, conventional controlled dosage forms delay the release of therapeutic systemic levels and do not provide a rapid onset of action. To modify the release of the drug from these systems, the surface area exposed to a fluid can be restricted by the addition of barrier layers to one or both sides of the tablets. However, most multilayer systems attempt to achieve a constant release rate from a tablet, not a biphasic release of the drug. When a single constant rate for drug release does not entirely satisfy the therapeutic objective, the immediate/slow delivery system may be an interesting alternative. This biphasic release system can be achieved by the application of an immediate release layer to the conventional layered matrix tablet. Recently, Li and Zhu, using combinations of versatile minitablets (rapid release, sustained release, pulsatile, and delayed onset sustained with various releasing lag times), obtained a multifunctional and multiple-unit oral drug delivery system, including a quick/slow release system.



Bi-Layer Tablets:

Bi-layer tablet is a new era for the successful development of controlled release formulation along with various features to provide a way of successful drug delivery system. Bi-layer tablet is better than the traditionally used mouthwash, sprays, and gels. Bi-layer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablet in which one layer is immediate release an initial dose and the second layer is maintenance dose. Bi-layer tablet is improved beneficial technology to overcome the shortcoming of the single-layered tablet. There is the various application of the bi-layer tablet it consists of monolithic partially coated or multilayered matrices. In the case of bi-layer 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.

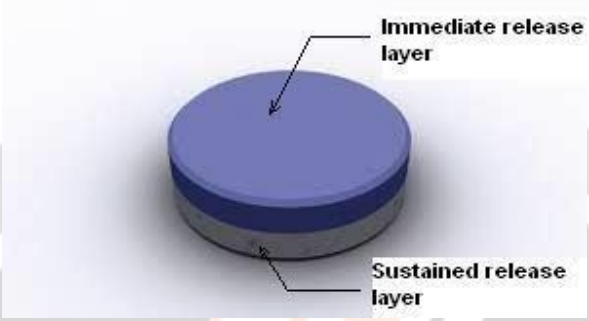


Figure 1.3 Image of Bi-Layer Tablet

Usually, conventional dosage form produces wide-ranging fluctuation in drug concentration in the blood stream and tissues with consequent undesirable toxicity and poor efficiency. Thus factors such as repetitive dosing and unpredictable absorption led to the concept of controlled drug delivery systems. The goal in designing sustained or controlled delivery system is to reduce the frequency of the dosing or to increase the effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery.

- **Need of bi-layer tablets**

1) For the administration of fixed-dose combinations of different active pharmaceutical ingredient (API), prolong the drug product lifecycle, buccal/ mucoadhesive delivery systems; fabricate novel drug delivery systems such as chewing device and floating tablets for gastro-retentive drug delivery.
2) Controlling the delivery rate of either single or two different active pharmaceutical ingredients.
3) To modify the total surface area available for the API layer either by sandwiching with one or two inactive layers in order to achieve swellable/erodible barriers for modified release.
4) To separate incompatible API from each other, to control the release of API from one layer by utilizing the functional property of the other layer (such as osmotic property).

- **Advantages of the bi-layer tablet.**

1. Bi-Layer execution with an optional single-layer conversion kit.
2. Cost is lower compared to all other oral dosage forms.
3. Greatest chemical and microbial stability overall oral dosage form.
4. Objectionable odor and bitter taste can be masked by a coating technique.
5. Flexible concept.
6. They are unit dosage form and offer the greatest capabilities of all oral dosage form for the greatest dose precision and the least content variability.

7. Easy to swallow with least tendency for a hang-up.
8. Suitable for large-scale production.

- **Disadvantages of bi-layer tablet.**

1. Some drugs resist compression into dense compacts, owing to amorphous nature, low-density character.
2. Bitter testing drugs, drugs with an objectionable odor or drugs that are sensitive to oxygen may require encapsulation or coating.
3. Difficult to swallow in case of children and unconscious patients.
4. Drugs with poor wetting, slow dissolution properties, optimum absorption high in GIT may be difficult to formulate or manufacture as a tablet that will still provide adequate or full drug bioavailability.

2.REVIEW OF LITERATURE

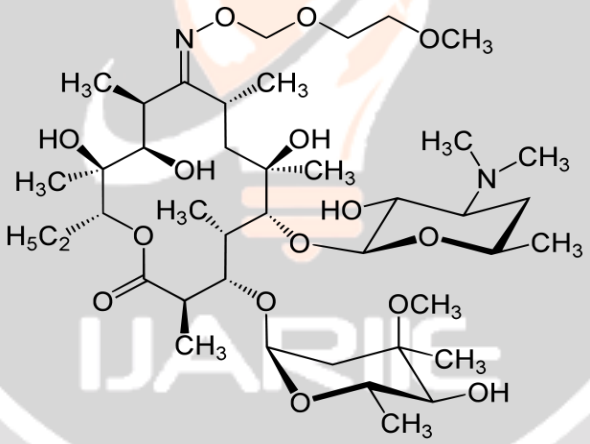
- **Shah et al. (2000)** investigated a mixture of polymeric coated, sustained release acetaminophen particles and uncoated, quick release acetaminophen particles pressed together in a tablet. Preferably, the coating is water permeable but is not Soluble or pH dependent. In another aspect of the invention, other pharmaceutical agents can be substituted for acetaminophen in the foregoing mixture, using the water-permeable, water-insoluble, pH-independent coating. Finally, the invention alternatively encompasses acetaminophen in Sustained release form per Se, coated with Said water-permeable, water-insoluble, pH-independent coating.
- **Han et al. (2003**) investigated a pharmaceutical dosage form having an immediate release component and a controlled release component. The controlled release component comprises a ratio of carbidopa to levodopa of from about 1:1 to about 1:50 such that the in vitro dissolution rate of the controlled release component is from about 10% to about 60% levodopa released after 1 h; from about 20% to about 80% levodopa released after 2 h; and from about 30% to about 99% levodopa released after about 6 h according to measurements under the USP paddle method of 50 rpm in 900 ml aqueous buffer at pH 4 at 37 °C.
- **Lim et al. (2004)** discovered a dosage form that includes a core from which drug is released on a prolonged basis and a coating or layer from which drug is released on an immediate-release basis can be made in a manner that provides a high degree of uniformity in the immediate release portion, even when the drug in the immediate-release portion is either insoluble or only sparingly Soluble in water. The coating or layer is either the particles themselves, applied as an aqueous Suspension, or a Solid composition that contains the drug particles incorporated in a Solid material that disintegrates rapidly in gastric fluid.
- **Carla Martins Lopes et al. (2007)** compressed Matrix Core Tablet as a Quick/Slow Dual-Component Delivery System Containing Ibuprofen. A dual component tablet made of a sustained release tableted core and an immediate release tableted coat was prepared by direct compression. The in vitro drug release profile from these tablets showed the desired biphasic release behavior: the ibuprofen contained in the fast releasing component was dissolved within 2 min, whereas the drug in the core tablet was released at different times (≈16 or 924 h), depending on the composition of the matrix tablet. Based on the release kinetic parameters calculated, it can be concluded that the HPMC core was suitable for providing a constant and controlled release (zero order) for a long period of time.
- **Geeta M. Patel et al. (2009)** compressed matrix dual-component vaginal drug delivery system containing metoclopramide hydrochloride. The purpose of the present investigation was to produce a quick/slow biphasic delivery system for metoclopramide hydrochloride using the superdisintegrantAc-di-sol for the fast release layer and hydroxypropylmethylcellulose K100M and Ucarflock 302 to modulate the release of the drug. The results of the full factorial design indicate that a small amount of HPMC K100M and a large amount of Ucarflock 302 favor sustained release of the metoclopramide hydrochloride vaginal dual component system. The *ex vivo* residence time reveals that the formulation was retained for more than 10 h.

- **Patel Geeta M et al. (2010)** formulated and evaluated once a Day Regioselective Dual Component Tablet of Atorvastatin Calcium and Metoprolol Succinate. The aim of the present investigation was to develop and evaluate Atorvastatin calcium (ATC) & Metoprolol succinate (MP) in the same dosage form, so there is no need to take an individual dosage form. HPMC K100M and polyox WSR N-60K sustained the release of Metoprolol succinate from the controlled release layer for more than 20 h. Diffusion exponents (n) were determined for all the formulations (0.45-0.89), so predominant drug release mechanism isnon-Fickian (anomalous) transport.
- **Alexander M et al. (2011),** investigated for a treatment where it is desired that an active agent is designed to be released immediately following administration and again at a time point some time after administration of the active agent. The present invention provides a NSAID agent such as diclofenac, formulated as a component of a presscoated tablet for alleviating pain and/or inflammation, wherein the tablet is intended to be administered immediately prior to a subject going to sleep and where in a portion of the NSAID is initially to be released immediately following administration and a further portion is released following a period of delay after administration.

Drug Profile:

➢ **Roxithromycin**

- **Chemical Formula:** $C_{41}H_{76}N_2O_{15}$
- **Chemical name:** (3*R*,4*S*,5*S*,6*R*,7*R*,9*R*,11*S*,12*R*,13*S*,14*R*)-6-[(2*S*,3*R*,4*S*,6*R*)-4-d-3-hydroxy-6-methyloxan-2-yl]oxy-14-ethyl-7,12,13-trihydroxy-4[(2*R*,4*R*,5*S*,6*S*)-5-hydroxy-4-methoxy-4,6-dimethyloxan-2-yl]oxy-10 (2methoxyethoxymethoxyimino)-3,5,7,9,11,13-hexamethyl-1oxacyclotetradecan-2-one
- **Structure:**



- **Molecular Weight:** 837.04
- **Physical appearance:** white crystalline type powder
- **Solubility:** Very slightly soluble in water; freely soluble in alcohol, in acetone, and in dichloromethane.
- **Melting point:** 111.0 – 118.0 °C
- **pK_a:** 9.27 at 25 °C
- **BCS Class (18):** class IV
- **Indication:** Used to treat respiratory tract, urinary and soft tissue infections
- **Mechanism of action:** Roxithromycin prevents bacteria from growing, by interfering with their protein synthesis. Roxithromycin binds to the subunit 50S of the bacterial ribosome, and thus inhibits the translocation of peptides. Roxithromycin has a similar antimicrobial spectrum as erythromycin but is more effective against certain gram-negative bacteria, particularly Legionella pneumophila.
- **Absorption:** Very rapidly absorbed and diffused into most tissues and phagocytes.
- **Metabolism:**Roxithromycin is only partially metabolized, more than half the parent compound is excreted unchanged. Three metabolites have been identified in urine and feces: the major metabolite is

descladinoseroxithromycin, with N-mono and N-di-demethylroxithromycin as minor metabolites. The respective percentage of roxithromycin and these three metabolites are similar in urine and feces.

- **Half-life:** 12 h **Protein binding:** 96%, mainly to alpha1-acid glycoproteins

3.AIM & OBJECTIVES

➢ **Aim:** Formulation and evaluation of Roxithromycin tablet for Upper Respiratory Tract Infection**.**

➢ **Objectives:**

- To develop quick and slow release biphasic system of macrolides and mucolytics for management of upper respiratory tract infection.
- To obtain a quick release of macrolides using disintegrants.
- To study the influence of different polymers on the release of mucolytics to achieve the adequate release of drug up to 12 h.
- To evaluate the dosage forms for different parameters for its suitability as an adequate dosage form.

4.PLAN OF WORK

A. Preformulation Studies:

Preformulation investigations are designed to identify those physicochemical properties and excipients that may influence the formulation design, method of manufacture, and pharmacokinetic and biopharmaceutical properties of the resulting product. Following tests to be performed for the preformulation study [28,31]

i. Solubility of drug
ii. Particle size
iii. Bulk density
iv. Tapped density
v. Carrs index & Hausner's ratio
vi. Flow property
vii. FT IR Spectroscopy
viii. Melting Point
ix. Drug -Drug Compatibility study

B. Formulation of Sustained Release Tablets.

The tablets to be formulated by using four different methods:

i. Direct Compression
ii. Wet Granulation
iii. Dry Granulation

C. Evaluation of tablets:

i. Appearance
ii. Weight variation
iii. Thickness
iv. Friability test
v. Hardness
vi. Disintegration test
vii. Dissolution test

D. Application of statistical tools and other software such as factorial design, for data analysis and interpretation.

5.MATERIALS & EQUIPMENTS

- **Materials**

Sr. No.	Drug and Ingredients
1	Roxithromycin
2	Hydroxypropyl Methylcellulose (HPMC K4M)
3	Ethyl cellulose (4 premium grade)
4	MCC (Avicel PH 101)
5	Sodium starch glycolate
6	PVP K30

Table 1: List of materials used

- **Equipments**

Sr. No.	Drug and Ingredients	Supplier
1	HPLC (LC-2010 CHT)	Shimadzu, Japan
2	Rotary tablet machine	Hardik machines, Ahmedabad, India
3	Dissolution test apparatus	USP 6 type apparatus, Electrolab, India
4	Monsanto hardness tester	Janki Impex Pvt. Ltd., Ahmedabad, India
5	Friabilator	Electrolab, India
6	Differential Scanning Calorimetry	Shimadzu, Japan
7	Weighing balance	Sartorius Weighing India Pvt. Ltd, New Delhi.

Table 2: List of instruments used

6..Experimental Work.

➢ **Preformulation study.**

Preformulation testing is the first step in the development of dosage forms. It is the study of physical and chemical properties of drug substance, derived properties of powder drug and compatibility study with excipients.

- **Organoleptic Properties**

This includes a recording of color, odor, and taste of the new drug using descriptive terminology.

- **Determination of melting point**

The melting point of drugs was determined by capillary method & compare with the reported value.

- **Solubility**

An excess amount of drug was added to distilled water containing flask then shake the flask until equilibrium is established for 24 h. Then filter this suspension, discarded the first 2 mL of the filtrate, then analyzed the drug in the filtrate. The concentration is considered the saturation or equilibrium solubility of the drug. The temperature of the solution should be kept at 25 ºC. The solubility of ambroxol hydrochloride and roxithromycin were tested in various solvents such as distilled water, 0.1N HCl and pH 6.8 Phosphate buffer.

- **Drug - Excipients Compatibility Study by Differential Scanning Calorimetry (DSC)1**

The compatibility study between drug and excipient was carried out to check whether it compatible or not. A differential scanning calorimeter (Shimadzu, Japan) was used for this study. Compatibility between ambroxol hydrochloride – roxithromycin and ambroxol hydrochloride - polymers were carried out at the temperature range of 50 – 300°C under nitrogen atmosphere. A 10 ºC/min heating rate was selected and thermogram obtained. Thermo gram of pure drug and mixture were studied for possible interaction.

➢ **Pre-compression parameters:**

- **Angle of repose:**

This angle is applicable for both pellets and lubricated blend. The angle of internal friction is a measure of internal stress distribution and is the angle at which an applied stress diverges as it passes through the bed. It is the least slope at which a powder will slide down an inclined plane surface. The typical method is to discharge the powder in a tapering mountain on a leveled even surface and compute the integrated angle with the level. It is denoted by θ.

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

Angle of repose (θ)	Flowability
<20	Excellent flow
20-30	Good flow
30-40	Passable flow
>40	Very poor flow

Table: Angle of repose

- **Bulk Density (BD):**

Exactly weigh amount of sample, and cautiously put into graduated cylinder. It had been prepared consistent exclusive of unsettling it. Afterwards bulk volume was calculated straight commencing the marks lying on the graduated cylinder as ml. Then the bulk density is computed with followed formula**:**

Bulk density = Weight of sample /Bulk volume

- **Tapped Density (TD):**

Tapped density is weight of sample divided by volume occupied by it. The lubricated sample or blend is tapped in cylinder at a certain height until constant volume is obtained and thus it is calculated further.

$$\square_{tapped} = \frac{m}{V\ tapped}$$

- **Compressibility index (CI) and Hausner ratio (HR):-**

Percent compressibility can be determined from the formula. $\frac{\rho_t - \rho_0}{\rho_t}$. CI= X 100

Where, ρ_t = Tapped density

ρ_0 = Bulk density

CI = Compressibility index

Compressibility index	Flow character
10	Excellent
11-15	Good
16-20	Fair
21-25	Passable
26-31	Poor
32-37	Very poor
>38	Very very poor

Table: Relationship between % compressibility and flowability

- **Hausner ratio:-**

It provides an indication of the degree of densification which could result from vibration of the feed hopper.

Hausner ratio	Flow character
1.00-1.11	Excellent
1.12-1.18	Good
1.19-1.25	Fair
1.26-1.34	Passable
1.35-1.45	Poor
1.46-1.49	Very poor
>1.60	Very very poor

Table: Hausner ratio and flow character

- **Particle size distribution:-**

This practice was done for the pellets obtained after drug coating and enteric coating to check average size of the pellets. 20 gms of the pellets were shifted in to sieve shaker, the machine was run for 5 minutes at 100 power, all the

sieves from ASTM sieve # 20 to 60 were taken out and collected the retained pellets by respective sieve and the % retention of pellets by that sieve was calculated.

➢ **Method of preparation**

Dual release bi-layer tablets were prepared by direct compression method.The ingredients were accurately weighed and mixed by triturating in a glass mortar and pestle. Pass this mass through 60 # sieve. The quantity of powder for the fast release layer was compressed lightly using a rotary compression machine (Hardik engineering, India) equipped with 12 mm diameter flat punches. Over this compressed layer, the required quantity of the sustained release layer was placed and compressed to obtain hardness in the range of 5 - 6 kg per cm^2 to form a bi-layer matrix tablet. The compositions of preliminary trial batches of the immediate release layer and the sustained release layer.

Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)
Roxithromycin	300	300	300	300	300	300
Sodium starch glycolate	30	30	30	30	30	30
PVP K30	20	20	20	20	20	20
MCC	140	140	140	140	140	140
Talc	5	5	5	5	5	5
Mg. stearate	5	5	5	5	5	5
Tablet total Weight	500	500	500	500	500	500

Table: Composition of Roxithromycin tablet

➢ **Post compression parameters:**

- **Weight Variation Test**

The weight variation test was done by weighing 20 tablets individually, calculating their average weight and comparing the individual weights to the average weight obtained.

The following formula was used to calculate the % deviation:

$$\% \text{ Deviation} = \frac{(Average\ Weight - Individual\ Weight)}{Average\ Weight} x100$$

- **Hardness**

Tablets require a certain amount of strength or hardness and resistance to friability, to withstand mechanical shocks of handling during manufacture, packaging and shipping. The Inweka hardness tester was used to check the hardness of random 20 prepared tablets.

- **Friability test**

The friability was determined by first weighing 10 tablets after dusting and placing them in a Roche friabilator, which was rotated for 4 min at 25 rpm. After dusting, the total remaining mass of the tablet was recorded and the percent friability was calculated using the following formula:

$$\textbf{Friability test} = \frac{\textbf{Weight of tablets before test} - \textbf{weight after test}}{\textbf{weight of tablets after test}} / 100$$

Acceptance of tablet was done when the maximum loss of weight was not greater than

1.0 % .

- **Thickness**

The thickness of the tablet was mostly related to the tablet hardness and was used as an initial control parameter. The thickness of the tablets was measured using vernier callipers. Twenty tablets were randomly selected.

- **Drug content**

Ten tablets were finely powdered and an amount equivalent to 75 mg of ambroxol hydrochloride was accurately weighed and transferred to a 100 mL volumetric flask; 70 mL of 0.1 N HCl was then added. The flask was shaken for 10 min. Finally, the volume was made up to the mark with 0.1 N HCl. The mixture was then filtered and measured by high-performance liquid chromatography (LC - 2010 CHT), Shimadzu, Japan. The method to quantify ambroxol hydrochloride and roxithromycin were done by HPLC with Phenomenex C18 column. The mobile phase consisted of an Acetonitrile: Phosphate buffer pH 5 in the ratio of 65:35. The liquid flow rate of HPLC was 1 mL/min. The wavelength of detection was 210 nm.

- ***In-vitro* Drug Release Studies.**

The *in-vitro*dissolution studies were carried out using USP 6 dissolution apparatus type - II (paddle method) at 50 rpm. Dissolution test was carried out for a total period of 12 h using 0.1N HCl (pH 1.2) solution (750 mL) as a dissolution medium at 37 ± 0.5° for first 2 h, and then addition of 0.2 M tribasic sodium phosphate to achieve pH 6.8 (1000 mL) for the rest of the period. Five mL of the sample was withdrawn at regular intervals and replaced with the same volume pre-warmed (37 ± 0.5°) fresh dissolution medium. The samples withdrawn were filtered through 0.45 µ membrane filter, and suitable dilution made. The drug content in each sample was analyzed by high-performance liquid chromatography (LC - 2010 CHT), Shimadzu, Japan. The wavelength of detection was 210 nm.

7.RESULTS AND DISCUSSION.

- **Calibration Curve of Roxithromycin**

The peak area for a standard solution of roxithromycin. The peak area of the standard solution is gradually increasing as increasing concentration of the drug. The calibration curve of drug. The regression coefficient was found to be 0.997.

Table: Calibration Curve of Roxithromycin

Sr. No.	Concentration (µg/mL)	Peak Area*
1	40	1217.33 ± 2.52
2	80	3360.33 ± 5.03

3	120	5249.67 ± 10.02
4	160	7494.33 ± 5.13
5	200	9432.33 ± 2.52
6	240	11840.67 ± 10.07
7	280	13386.67 ± 6.51
* Values are expressed as mean ± SD; n=3, SD: Standard Deviation		

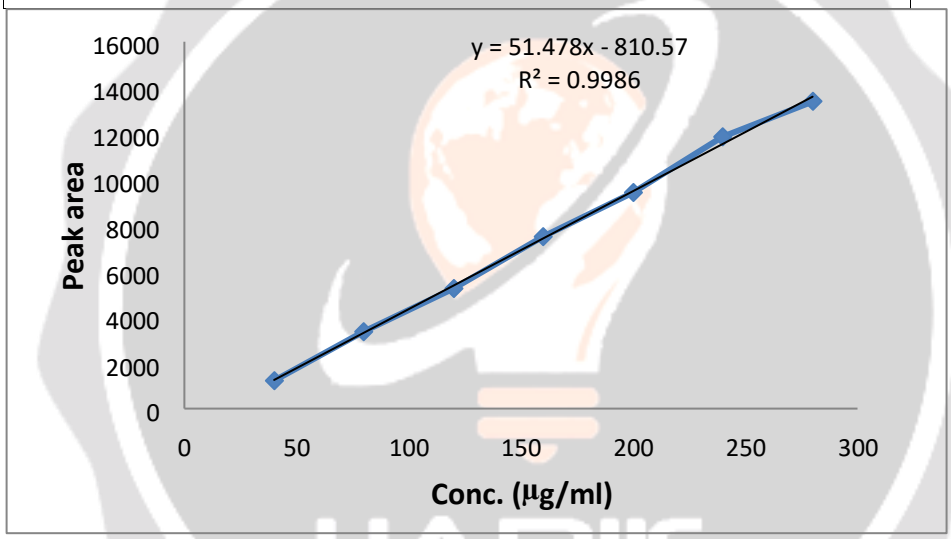


Figure: Calibration Curve of Roxithromycin

➢ **Preformulation Study**

- **Organoleptic Properties**

Roxithromycin is a white crystalline powder having bitter in taste.

- **Determination of Melting Point**

The practical value and theoretical value for the melting point of roxithromycin are describing. There is no significant difference between practical value and theoretical value for the melting point of drugs.

Table: Melting Point of Roxithromycin

Drug	Practically obtained	Theoretical range
Roxithromycin	117 °C	111 - 118 °C

- **Solubility**

The roxithromycin is soluble in Acetone, Ethanol, Chloroform, methyl chloride, DMSO.

Table: Solubility of Roxithromycin

Drug	Solubility in (mg/mL)		
	Water	0.1N HCl	6.8 pH phosphate buffer
Roxithromycin	0.02	69.5	0.02

- **Drug - Excipients Compatibility Study by Differential Scanning Calorimetry (DSC)**

The DSC thermograph of pure drug and mixture are shown in

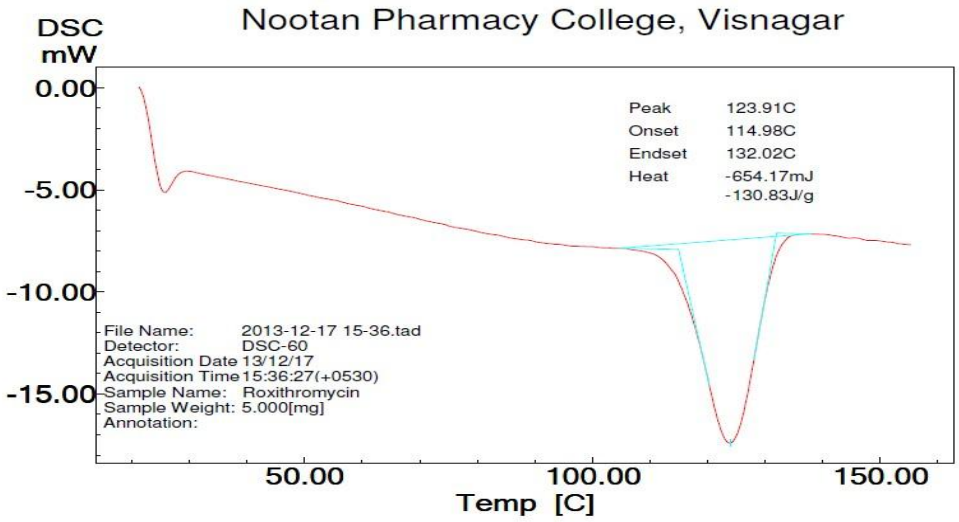


Figure: DSC of Pure Roxithromycin

➢ **Evaluation of Dual Release Tablets of Roxithromycin**

- **Physical Characterization of Dual Release Tablets**

The evaluation parameters of trial batches are shown in Table. The weight variation of prepared tablets is between 644.6 and 663.2, which is acceptable in range as per standard limit. Hardness and Friability data show that good mechanical property because the hardness of tablets is near to 5 kg/cm^2 and friability is less than 1%. The thickness of tablets is uniform and between 5.93 to 6.30 mm. Drug content shows the uniformity of drug in individual dosage forms. The roxithromycin is found to be in the range of 98.3 to 103.1%. The drug content is found to be a uniform and acceptable range.

Table: Evaluation of Prepared Tablets

Parameter	Batches					
	F1	**F2**	**F3**	**F4**	**F5**	**F6**
Weight variation	644.6 ±6.3	663.2 ±8.8	655.1 ±7.9	646.5 ±5.7	660.2 ±3.6	654.9 ±4.3
Assay (%)	98.3	99.2	103.1	99.4	100.4	98.5
Friability (%)	0.74	0.45	0.66	0.70	0.46	0.54
Hardness (kg/cm^2)	5.17 ±0.76	5.50 ±0.50	5.33 ±0.58	4.83 ±0.29	5.00 ±0.50	5.33 ±0.29
Thickness (mm)	6.30 ±0.10	6.17 ±0.15	6.23 ±0.21	5.93 ±0.06	6.03 ±0.06	6.07 ±0.21
* Values are expressed as mean ± SD; n=20						
# Values are expressed as mean ± SD; n=3, SD: Standard Deviation						

- ***In-vitro* drug release study**

The drug release of roxithromycin from prepared dual release tablet is shown in Figure. The roxithromycin was almost (> 95%) released at 15 min. which shows the quick drug release. The dissolution study was carried out up to 12 h. In the F3 batch, HPMC K4M is used in 60 mg quantity so the drug release is very slow and only 48% drug was released at 12 h. Release of drug in F1 batch containing 20 mg of HPMC K4M have good release up to 12 h. Fast drug release found in F4 batch containing 20 mg of ethyl cellulose, almost drug was released at 8 h. Slow drug release found in F6 batch containing 60 mg of ethyl cellulose. For optimization study, the amount of HPMC K4M was selected 10 to 30 mg and ethyl cellulose was selected 20 to 30 mg.

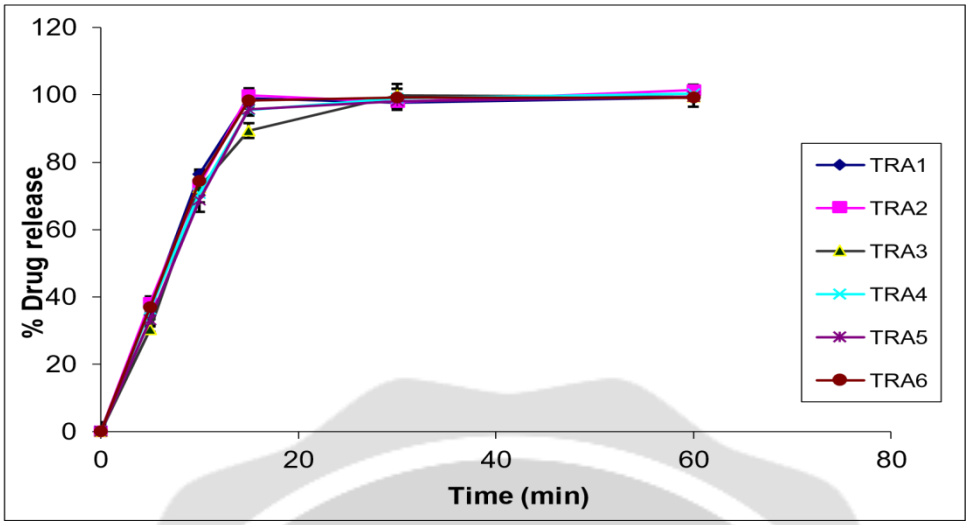


Figure: *In-Vitro* Drug Release of Roxithromycin from Prepared Tablets

8.CONCLUSION.

The dual release bi-layer tablets of roxithromycin were developed using sodium starch glycolate as a disintegrant for immediate release effect of roxithromycin. For the selection of concentration of polymers, trial batches were taken. The 3^2 factorial design was adopted to find out the optimum concentration of ethyl cellulose and HPMC K4M. The similarity factor with theoretical dissolution profile and percentage drug release at 10^{th} h selected as dependent variables and concentration of ethyl cellulose and HPMC K4M were selected as independent variables. As the concentration of HPMC K4M was increased, the drug release decreased and the effect of EC was found to be less compared to HPMC K4M. The amount of HPMC K4M and ethyl cellulose were found 19.0 mg and 29.8 mg, respectively for an optimized batch of factorial design. The kinetic mechanism of drug release follows zero order and Higuchi models to optimized batch. The stability study indicates that there were no significant changes after storage of dual release tablets for stability study.

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