STUDY ON DEVELOPMENT OF TASTE MASKED ROXITHROMYCIN ORAL SUSPENSION BY USING CATION EXCHANGE RESIN- INDION 204

THESIS

Submitted to The Tamilnadu Dr. M.G.R. Medical University, Chennai

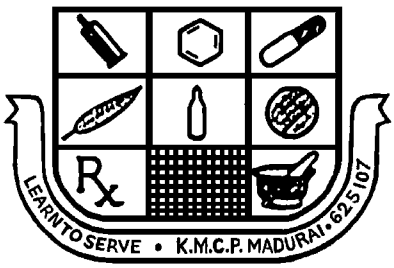
In partial fulfillment of the requirements

for the award of the Degree of

MASTER OF PHARMACY

IN

PHARMACEUTICS



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MARCH - 2009

CERTIFICATE

This is to certify that the dissertation entitled "**STUDY ON DEVELOPMENT OF TASTE MASKED ROXITHROMYCIN ORAL SUSPENSION BY USING CATION EXCHANGE RESIN- INDION 204**" submitted by **Mr. RAJNEESH PANDEY** to The Tamilnadu Dr. M. G. R. Medical University, Chennai, in Partial Fulfillment for the award of Master of Pharmacy in Pharmaceutics at K.M. College of Pharmacy, Madurai, is a bonafide work carried out by him under my guidance and supervision during the academic year 2008-2009.

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DEDICATED TO MY BELOVED PARENTS AND TEACHERS

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CHAPTERS. **PAGE NO.**

1.Introduction

1.1 Definition[1]

Suspension are heterogenous system containing of two phases the continuous or external phase is generally a liquid or semisolid, and the dispersed or internal phase in made up of matter that is essentially insoluble in, but dispersed throughout, the continuous phase: The insoluble matter may be intended for physiological absorption or for internal or external coating function. The disperse phase may consist of discrete particles, or it may be a network of particles resulting from particle – particle interactions.

1.2 PHARMACEUTICAL APPLICATIONS OF SUSPENSION[2]

Suspensions can be used as oral dosage forms, applied topically to the skin or mucous membrane surfaces, or given parentarally by injection.

Suspension as oral drug delivery systems:

Many People have difficulty in swallowing solid dosage forms and therefore require the drug to be dispersed in a liquid.

Some materials are required to be present in the gastro intestinal tract in a finely divided form, and their formulation, a suspension will provide the desired high surface area. Solid such as kaolin, Magnesium Carbonate and Magnesium Trisilicate are used for the adsorption of toxins, or to neutralize excess acidity. A dispersion of finely divided silica in dimethicone 1000 is used in veterinary practice for the treatment

of ‘Forthy bloat’. The taste of most drug is more noticeable if it is in solution rather than in an insoluble form.

Suspension for topical administration

Suspension of drugs can also be formulated for topical application. They can be fluid preparations, such as calamine lotion, which are designed to leave a light deposit of the active agent on the skin after quick evaporation of the dispersion medium. Some suspension, such as pastes, are semisolid in consistency and contain high concentration of powders dispersed usually in a paraffin base. It may also be possible to suspend a powered drug in an emulsion base, as in zinc cream.

Suspension for parenteral use and inhalation therapy:

Suspension can also be formulated for parenteral administration in order to control the rate of absorption of drug, by varying the size of the dispersed particles of active agent, the duration of activity can be controlled, the absorption rate of the drug into the blood stream will then depend simply in its rate of dissolution. If the drug is suspended in a fixed oil such as arachis or sesame, the product will remain after injection in the form of an oil globule, thereby presenting to the tissue fluid a small surface area from which the partitioning of drug can occur. The release of drug suspended in the aqueous vehicle will be faster, as some diffusion of the product will occur along muscle fibers and become miscible with

tissue fluid. This will present a larger surface area from which the drug can be released.

The adsorptive properties of fine powders are also used in the formulation of some inhalation the volatile components of menthol and eucalyptus oil would be lost from solution vary rapidly during use, whereas a more prolonged release obtained if the two active agents are adsorbed on to light magnesium carbonate prior to the preparation of a suspension.

1.3 FLOCCULATED AND DEFLLOCULATED SYSTEMS[3]:

Having incorporated a suitable wetting agent, it is then necessary to determine whether the suspension is flocculated or deflocculated and to decide which state is preferable whether or not a suspension flocculated or deflocculated depends on the relative magnitude of the forces of repulsion and attraction between the particles. The effect of these particle – Particle interaction have been adequately covered.

In a deflocculated system the dispersed particles remain as discrete units and, because the rate of sedimentation depends on the size of each unit, settling will be slow. The supernatant of a deflocculated system will continue to remain cloudy for an appreciable time after shaking, due to the very slow settling rate of the smallest particles in the product, even after the larger ones have sedimented. The repulsive forces between individual particles allow them to slip fast each other as they sediment.

The slow rate of settling prevent the entrapment of liquid within the sediment. Which thus becomes compacted and can be very difficult to redisperse. This phenomenon is also called caking or claying, and is the most serious of all the physical stability problem encountered in suspension formulation.

The aggregation of particles in a flocculated system will lead to a much more rapid rate of sediemention or subsidence because each unit is composed of many individual particles and is therefore larger. The rate of settling will also depend on the porosity of the aggregate, because if it is porous the dispersion medium can flow through, as well as around each aggregate or flocculated as it sediments.

In a flocculated system the supernatant quickly becomes clear, as the larger flocs that settles rapidly are composed of particles of all size range the appearance of both flocculated and deflocculated suspension at given time after shaking.

In summary, deflocculated systems have the advantage of a slow sedimentation rate, there by enabling a uniform dose to be taken from the container, but when settling, does occurs the sediment is compacted and difficult to redisperse. Flocculated systems form loose sediments which are easily redispersible but the sedimentation rate is fast and there is a danger of an in accurate dose being administered also the product will look inelegant.

Controlled flocculation:

A deflocculated system with a sufficiently high viscosity to prevent sedimentation would be an ideal formulation. It can not be guaranteed, however, that the system would remain homogenous during the entire shelf – life of the product usually a compromise is reached in which the suspension is partially flocculated to enable adequate redispersion if necessary,and viscosity is controlled so that the sedimentation rate is at a minimum.

The next stage of the formulation process after the addition of the wetting agent is to ensure that the product exhibits the correct degree of flocculation. Under flocculated will give those undesirable properties that are associated with deflocculated systems. An over flocculated product will look inelegant and to minimize settling, the viscosity of the product may have to be so high that any necessary redispersion would be difficult controlled flocculated is usually achieved by a combination of particle size control the use of electrolytes to control zeta potential of the addition of polymer to enable cross linking to occur between particles. Some polymer have the advantage of becoming ionized in an aquous solutions and can therefore at both electro statically stearically. These materials are also termed poly electrolytes.

1.4. RHEOLOGY OF SUSPENSIONS[4]:-

An ideal pharmaceutical suspension would exhibit a high apparent viscosity at low rates of shear so that on storage the suspended particles would either settle very slowly or preferably remain permanently suspended. At high rates of shear such as those caused by moderate shaking of the product the apparent viscosity should fall sufficiently for the product to be powered easily from its container. The product if for external use should then spread easily without excessive dragging, runs off the skin surface. If intended for injection the product should pass easily through a hypodermic needle with only moderate pressure applied to the syringe plunger it would then be important to be reformed after a short time to maintain adequate physical stability.

A flocculated system partly fulfils these criteria in such a system pseudo plastic behavior is exhibited as the structural progressively breaks down under shear. The product then shows the time dependent reversibility of this loss of structure which is termed thixotropy.

A deflocculated system however would exhibit Newtonian behavior owing to absence of such structures and may even if high concentration of disperse phase are present exhibit dilatancy.

Although a flocculated system may exhibit some thixotropy and plasticity, unless a high concentration of disperse phase is present it may not be sufficient to prevent rapid settling particularly if a surfactant or an

electrolyte is present as a flocculating agent in these cases suspending agents may be used to increase apparent viscosity of the system.

Suitable materials are the hydrophilic polymers discussed above. These exerts their effect by entrapping the solid dispersed particles within their gel like network so preventing sedimentation. At low concentration many suspending agents can be used to control flocculation and it must be realized that if large quantities are to be used to enhance viscosity the degree of flocculation may also be altered.

1.5. CHARACTERISTICS OF ORAL AQUEOUS SUSPENSION

Efficacy[5]:-

Drug suspension are often very effective pharmacologically and are less complicated to manufacture than other dosage forms. Their effectiveness may be attributed to a number of factors. For example, drug formulated as suspension are more bioavailable than tablets or capsules. Bioavailable versus the solid dosage formulation may also be enhanced by decreasing the particle size of the drug.

Suspensions are often more effective than tablets and capsules in the paediatric and geriatric patients. These patients generally find suspensions easier to swallow and also dose flexibility.

Desired Attributes:-

Aqueous suspension are defined as systems of insoluble drug dispersed in a water vehicle. In addition to drug, a typical suspension may contain several other ingredients including wetting agent suspending agent, protective colloid, flocculating agent, sweetener,preservatives, buffer system, flavour, colour, sequestering agent and antifoaming agent.

1.6. PRINCIPLES OF FORMULATION[6]

Since the specific properties of various suspending drugs differ, no single procedure will always produce a successful suspension product. Different methods have been developed with varying degree of success. However certain principles have been recognized that are fundamental in all successful formulations.

Particle size:-

It is an important consideration for the physical stability of the suspension. As the insoluble drug settles, a nonuniform distribution results. A major goal of the formulation is to slow or even prevent the sedimentation of the drug particles. The relationship of factors that describes the race of particles settling or sedimentation is stoke's law.

$V = d^2(P_1 - P_2)\ g/18$

Where,

V = Sedimentation rate of average particle

d = Mean Particle diameter

P_1 = Particle density

P_2 = Density of the dispersion medium

g = acceleration due to gravity

n = Viscosity of the dispersion medium

The above equation illustrates that the sedimentation rate is directly proportional to the square of particle diameter and therefore small particles settle slower than longer settling. In addition particle – Particle interactions can also have a significant effect on suspension stability.

For suspension with a relatively high percentage of solids interparticle interaction may produce more viscous or thixotropic dispersions smaller particles will have a high surface area/weight ratio that favours interactions between the particles and may produce desirable rheological characteristics.

In addition to the effects on the physical properties of a suspension particle size has important implications on the biopharmaceutical performance of the drug. For drugs whose solubility in water is slow, the dissolution rate of the drug particles may be primary factor that limits absorption of the drug. In these cases, the rate and extent of absorption of the drug may be enhanced, through the use of the particles of small diameter. Small particles dissolve faster than larger particles due to the increased surface area per unit weight of drug of the former.

Some Drugs will pose problems such as particle size reduction and polymorphism and crystal growth to formulation in most pharmaceutical suspensions the range of particle size reduction dry milling, spray drying, micro pulverization and fluid energy grinder.

Viscosity:-

Stokes law illustrates the inverse relationship between viscosity of the dispersion medium and rate of particle settling. An increase in viscosity produces a slower sedimentation rate and increase physical stability. Viscosity is also increased by the volume fraction of particles, the most common method of increasing viscosity is by adding a suspending agent. Too high a viscosity is undesirable, it interferes with pouring and redispersal of settled particles.

According to stoke's law, sedimentation rate is also lowered by reducing the density difference between the particles and the dispersion medium. The control of sedimentation is important in maintaining the integrity of a dispersion system. Stokes law defines the sedimentation rate of sphere in a fluid as

$$Sr = 2ga^2 (ds - dl)\ 9n$$

Where,

Sr = Sedimentation rate

ds = Density of sphere

dl = Density of liquid

a = Particle size

n = Viscosity of continuous phase.

Although most days in suspension are not perfect spheres and the suspension are not dilute enough to follow stoke's law the equation is still useful. From the equation three methods of controlling sedimentation are

i) Particle size reduction

ii) Density matching

iii) Viscosity building

If the density of the medium and the suspended particles are same, sedimentation will not occur. The rheological characteristics of the polymer solutions used to sterilize disperse system are very important.

Viscosity aging effects:

The shelf life of a dispersion depends on the chemical stability of its ingredients as well as the physical stability of the system. Several factors that may be responsible for changes in dispersion viscosity over a period of time. Some are obviously due to alteration with rest of the system.

Particle growth may be independent of polymer content, although polymers present may reduce the rate of change of particle size.

Depolymerization results in a decrease in organization. Molecular weight, hence decrease in viscosity.

Depolymerization occurs while processing under high shear chemical changes in the system over time, producing a drift in pH or generating ionic products may alter viscosity. Polymers may introduce a second order effect on viscosity by acting as either flocculating or deflocculating agent. Because of variety of factors that an alter viscosity over times, some of which increase viscosity while others have opposite effect. Small drifts in apparent viscosity are often encountered however substantial changes are cause for concern because of changes in the resistance to sedimentation and also because they suggest that chemical or physical changes of some kind are taking place.

Causes of change in viscosity in disporse system upon storage.

Cause	**Usual effect on viscosity**
Depolymerization	Reduction
Particle growth	Reduction
Slow polymer hydration	Increase
Chemical change dispersion	Variable
Increase in flocculation	Increase

Wetting:-

Hydrophilic drugs are easily wetted by water or other polar liquids. They may also greatly increase the viscosity of water suspensions and are incorporated into suspensions without the use of wetting agents. Most drugs are hydrophobic and when suspended, frequently float on the vehicle surface due to poor wetting.

A wetting agent enhances the ability of the dispersion medium or suspension vehicle to spread on the surface of the drug particles by reducing the interfacial tension between solid particles and vehicles. Low concentrations of surfactants are commonly used. Excess concentrations may lead to foaming or unpleasant taste.

An addition caution with wetting agents is the increased possibility of caking, since the coated particles resists aggregate formation, settle individually and may form a dense sediment.

Mixing:-

It is the major operation of suspension preparation. It is very important since inadequate mixing results in non homogeneity of the drug dispersed in the vehicle if the drug is hydrophobic, a wetting agent should be included. Sometimes shearing forces from ball mill or colloid mill are used to break up particles aggregates for better wetting and dispersion of drug.

The addition of suspending agent such as carboxymethyl cellulose to build viscosity increases the difficulty of mixing. The equipment

must have the capacity to mix but the excessive shearing and its heat can fracture polymeric suspending agent and should be avoided often the completed suspension is passed through a colloid mill to break up excessive particle aggregates and to ensure adequate mixing of the final product.

Flocculation:-

It is the process, in which the particles are allowed to come together and formation of loose particle aggregates. The floc settle and produce a sediment which is less dense and easier to resdisperse. If the flocculated particles have a sufficient concentration prior to settling, a continuous structure is produced which results in yield Value and little sedimentation. The yield value can be used as indicator for the extent of flocculation.

The material used to produce flocculation in suspension namely electrolytes, surfactants and polymers. Electrolytes act as a flocculating agent by reducing the electric barrier between the particles, as evidenced by a decrease in the zeta potential and the formation of a bridge between adjacent particles so as to link them together in a loosely arranged structure.

Surfactants both ionic and non-ionic, have been used to bring about flocculation of suspended particles.

Polymers are long-chain, high molecular-weight compounds containing active groups spaced along their length. These agent act as flocculating agents because part of the chain is adsorbed on the particle surface, with the remaining parts projecting out into the dispersion medium. Bridging between these latter portions leads to formulation of flocs.

1.7 Commonly used ingredients/Additives[7]:-

The term 'additive' refers to those components of a formulation which do not posses any therapeutic activities and which generally facilitate the stability, use or manufacture of a formula. These additive may have an effect in the physicochemical stability of the formulae and on the bioavailability of the drug.

Suspending Agent:-

These agents are used to impart greater viscosity and retard sedimentation factors to consider during selection include suspending ability in the system, chemical compatibility with a all ingredients, especially the drug, length of time for hydration, appearance, source, reproducibility of these consideration from batch to batch and cost.

These agents subdivided in to cellulose derivatives, clays, natural gums, synthetic gums miscellaneous agents.

Cellulose derivative:-

These derivatives are subdivided into cellulose, methylcellulose, ethyl cellulose and propyl cellulose group. These are semi synthetic have batch to batch reproducibility of their characteristic excluding sodium carboxy methyl cellulose, these are nonionic and their fore are chemically compatible with another ingredients, these agents exhibit pseudo plastic flow and have no yield value.

Clays:-

There are hydrated aluminium or magnesium silicate which is water hydrate further to form viscous colloidal dispersions, they exhibit thixotropy they are more stable between pH 9 to 11. Magnesium Aluminum silicate is extensively used in its innocuous taste often produces a more acceptable suspension. Bentonite, hectolite and attapulgite are the other examples. Silicon dioxide and its hydrates are considered because their colloidal nature is similar to that of clays.

Natural gums:-

Gums are water soluble and produce solution of high viscosity. There may be either non-ionic or anionic. Tragacanth solutions are very viscous and are stable over a wide range it exhibit pseudo plastic flow. Guar gum and locust bean gum are non-ionic.

Alginates exhibit Newtonian flow at low concentration it is highly viscous. Propylene glycol alginate is a non gelling form and exhibit pseudo plastic flow. Gum Arabic is water soluble with no solubility in organic solvents. Addition of ethanol to aqueous solution of gum Arabic rapidly decrease viscosity.

Xanthum gum is used as suspending agent because of its shear thining or pseudo plastic flow. Xanthum gum solving viscosity is almost independent of temperature and pH, this polymer is resistant to shear depolymerization.

Synthetic gums:-

These agents have the advantage of good batch to batch uniformity and no microbial contamination. Carbomer is widely used because its solution have high viscosity and a yield value. Povidone act as protective colloid. Complex formations with pvp has been used to modify the toxicity of certain drugs. Polyvinyl allow, the viscosity in low and are little affected by temperature.

Miscellaneous:-

Glycyrrhizin is reported to have good suspending characteristics its solution is pseudo plastic and exhibit thixotropy.

Flocculating Agents:-

These agents enable particles to link together in loose aggregates or flocs. These flocs settle rapidly but are early redispersed. These agents

are subdivided into – (a) surfaces (b) hydrophilic polymers (c) clays (d) electrolytes.

Surfactants:-

Both ionic and non-ionic surfactants are used as flocculating agents and the concentration employed range from 0.01 to 1.0% w/v non-ionic surfactants are preferred because they are chemically compatible with more ingredients

Hydro polymer:-

These have high molecular wt. with long carbon chains and include many material which at higher concentration are employed as suspend protective colloid to prevent caking and as a flocculating agent to form loose flocs.

Electrolyte:-

They can enhance flocculation and lower the necessary surfactants concentration.

Clays:-

Clays at concentration equal to or above 0.1% gives successful flocculation of most drugs suspended in a sorbitol or syrup base.

Wetting agents:-

The U.S.P. 25 includes 21 surfactant as official wetting agents or solubilizing agents surfactants may be described as material which

have a tendency to preferentially get located at the interfaces between two phase many lipophilic drugs are solubilized using surfactants for better bioavaibility surfactants having HLB values between 15 to 18 are considered to be good solubilizing agents increased distribution of many drugs due to miceller solubilization intestinal absorption of lipophilic drugs increase with non-ionic surfactants. Intestinal absorption of lipophilic drugs increases when tween – 80 is used as below concentration cmc and decreases when concentration above cmc.

Sodium carboxy methyl cellulose, bentonite, aluminium magnesium silicate and colloidal sillicon dioxide also aid the dispersion of hydrophobic drugs.

Glycerin, Propylene glycol are also used as wetting agents.

Sweetnerss:-

Sweeteners are added to produce a more palatable medications. Drugs have a bitter taste and the suspending agents particularly clay may have bland taste. A viscous sweetener sorbitol solution or syrup, can be used to impart viscosity to retained sedimentation.

The common sweetening agents include mannitol, aspartame and sodium saccharin, due to carcinogenic potential, saccharin in the united states remains on a year to year basis.

Additional Ingredients:-

Buffers:-

Buffers are used to control the pH of the formulation. The pH may be selected on the basis of solubility or stability of the drug, thebuffers used commonly are citric acid, sodium citrate and fumaric acid.

Flavours:-

It enhance the patient acceptance of the product. Some newer flavours used for children include. Raspberry, pineapple of bubble gum these agents are usually oils of require solvents.

Coloring agents:-

Colourants are intended to provide a more aesthetic appearance of the final suspension.

Preservative:-

Preservative are required in most suspensions because some natural gums are source of contamination and also the suspending agents and sweeteners are often good growth media for micro organisms. In some suspension drugs impart all is which no preservative is stable. Commonly used are butyl paraben, methyl paraben, propyl paraben and sodium benzoate.

1.8 EVALUATION OF SUSPENSION[8]:-

The method used for evaluating the physical stability of suspension may be categorized as sedimentation method, rheological methods, electro kinetic methods, micro meritic methods.

Sedimentation methods:-

The formation of the sediment and its resdispersibility are the two features related to the over all acceptability of suspension.

The simplest procedure for evaluation is to keep a measured volume of suspension in a graduated cylinder in an undisturbed state for certain period of time and volume of sediment is noted, which is expressed as ultimate height (HU). This is relation to the initial volume of the suspension (H0) is expressed as sedimentation ratio.

$F = Hu/Ho$

Where,

Hu = ultimate settled height of sediment

Ho = original height of sediment

F = sedimentation volume

Redispersibility can be estimated by shaking the suspension with the help of a mechanical device which stimulates motion of human are during shaking process and can give reproducible results when used under controlled condition.

Rheological Method:-

Evaluation of rheological behaviour of suspensions can help in predicting the settling pattern and can also provides due to vehicle particle structures. Generally lower shear rates are employed and samples are evaluated undisturbed. By the use of Brookfield viscometer with T. spindle is made to descend slowly in to suspension and the dial reading on the viscometer is then measure of the resistance the spindle meets at various level in a sediment. In this technique, the T-bar is continually changing position and measure undisturbed samples as it advances down into the suspension.

This technique also indicates in which level of the suspension the structure is greater, owing to particle agglomerating, because the T-bar descends as it rotates, and the bar is continually entering obtained on samples variously aged and stored place. Thus, using the T-bar spindle and the helipath, the dial reading can be against the number of turns of the spindle. This measurement is made on undisturbed samples of different ages. The result indicate how the particles are settling with time. In a screening study, the better suspensions show a lesser rate of increase of dial reading with spindle turns, i.e., the curve is horizontal for a longer period.

Electro kinetic methods:-

The surface electronic charge or zeta potential is instrumental in deciding the stability of disperse phase system. The measurement of migration velocity of particles by electrophoresis method that employed a micro electrophoresis appratus. Zeta potential produce more stable suspensions because aggregation was controlled and optimized.

Micro meritic methods:-

The stability of the suspension is inter related to the size of particles constituting to its disperse phase. A growth in the particle size will results in the formulation of lump or cake destroying the physical structure of a suspensions. Changes in the particle size distribution, crystal habit are determined by microscope and coulter counter.

1.9 Advantages[9]:-

1. Suspension are an ideal dosage form for patients who cannot swallow tablet or capsules.
2. Since it contains finely divided particles the rate of absorption is quicker.

Properties of a pharamaceutical suspension:-

1. Particles in suspensions are small and relatively uniform in size, so that the product is free from a gritty texture.
2. There is ready dispersion of any sediment on storage.

3. The suspension is pour able
4. After gentle shaking, the medicament stays in suspension long enough for a dose to be accurately measured.

CHAPTER 2

LITERATURE REVIEW OF TASTE MASKED SUSPENSION

Sambhaji pisal et al (2004), Formulated and evaluated the molecular properties of ciprofloxacin – Indion 234 complexes. The effect of batch and column process, complexation time, temperature, and pH on ciprofloxacin loading on indion 234 is reported. The drug – resin ration in complexes are 1:1.3and it is enhanced by pH and not affected by temperature. Indion 234 is inexpensive, and the simple technique is effective for bitterness masking of ciprofloxacin. [10]

Moshe gerold L et al (2005), formulated and evaluated taste-masked formulations containing sertraline and sulfoalkyl ether cyclodextrin. The liquid formulations are pleasant tasting convenient to use, and chemically and physically stable. This formulation provides significant advantages over the masked non-aqueous formulation and other cyclodextrin – containing formulation of sertaline.[11]

V.G.Jamakandi et al (2008), studied on usage and evaluation of stevioside as sweetening agent in salbutamol sulphate and bromhexin

hydrochloride syrups as concentration of 0.5 and 1.0% w/v. The usage of stevioside can offer many advantages to patients suffering from diabetes, phenylketonurea and calorie conscious, ranging from pediatrics to geriatrics.[12].

CGG Rao et al (2004), studied on formulation of taste masked oral suspension of quinine sulphate by complexation, which is very much effective against resistant strains of plasmodium falciparum where other antimalarials like chloroquine, sulphadoxine – pysimethamine are ineffective. But, it is very bitter drug and taste should be masked by complexation technique using ion exchange resin and to formulated into a suspension.[13]

Shah PP et al (2008), formulated and evaluated of taste masked oral reconstitutable suspension of primaquine sulphate by using beta – cyclodextrin catchets prepared using physical mixture (DS 24), showed complete bitter taste masking and easy redispersibility. [14]

Kiran Bhise et al (2008), reviwed on taste masked, design, evaluation of an oral formulation using ion exchange resin as drug carrier of diphenylhydramine hydrochloride and the cation exchange resin are used as Indion 234 and Tulsion 343 that contained cross linked polyacrylic backbone were used.[15]

Patel A R et al (2008), prepared and evaluated of taste masked famotidine formulation using drug / beta cyclodextrin polymer ternary

complexation as an approach for taste masking. Improvement in taste masking capability of cyclodextrin towards famotidin was evaluated by formulating a ternary complex including hydrophilic polymer HPMC as the third component result showed that the ternary complex better than binary complex.[16]

Bhalerao S.S. et al (2003), studies on sustained release liquid oral formulation of diltiazem hydrochloride : Reconstitutable suspension, microspheres of diltiazem hydrochloride were prepared by non-aqueous emulsion solvent evaporation technique using ethyl cellulose as an encapsulating polymer drug loaded microsphere were formulated into a redispersible suspension having sustained release charecteristics.[17]

LITERATURE REVIEW OF ROXITHROMYCIN FORMULATION

Eberi, s et al (2007) studied on pole of p-glycoprotein inhibition for drug interactions, in vitro, the effect of macrolides on polarized p-glycoprotein-mediated digoxin transport was investigated in caco-2 cells with concentrations producing 50% inhibition (IC 50) values of 1.8, 4.1, 15.4, 21.8 an 22.7 mu mol/L for telithromycin, clarithromycin, roxithromycin, azithromycin and erythromycin.[18]

Margaritis, VK et al (2007), studied the sinus fluid penetration of oral clarithromycin and azithromycin in patients with Acute rhino sinusitis, sinus fluid aspirates and serum sample collected 2, 4, 6, 8 and

12 hours after the Administration of three doses of oral clarithromycin 500 mg, twice daily or two doses of azithromycin 500 mg once a daily.[19]

Hang, TS et al (2007) studied the simultaneous determination and pharmacokinetic study of roxithromycin and ambroxol hydrochloride in human plasma by LC-MS/MS in 12 healthy male Chinese volunteers after an over night fast by a single dose (150mg), 30mg respectively way crossover design with a period of 7 days washout. No significant difference were observed for the major pharmacokinetic parameters such as C-Max, T-Max, t(1/2) and AUC of both roxithromycin and Ambroxol between different treatment.[20]

Yasuda Y et al (2007) studied the Roxithromycin favorably modifies the initial phase of resistance against infection with macrolide-resistant streptococcus pneumonia in a murine pneumonia model, among the macrolides tested, only roxithromycin did not affect in vitro pneumococcal virulence factors at sub-MIC levels.[21]

Oyama T et al (2007), studied the Roxithromycin inhibits tumor necrosis factor-alpha-induced matrix metalloproteinase-1 expression through regulating mitogen-activated protein kinase phasphorylation and ETS-1 expression in human periodontal ligament cell cultures, cultured cells were incubated with 1% fetal bovine serum for 24hr, followed by treatment with 10kg/ml TNF-alpha, roxithromycin, and mitogen – activated protein kinase inhibitor at various concentration.[22]

Woessner R et al (2006), studied the long term antibiotic treatment with roxithromycin in patients with multiple sclerosis. In study investigated a possible therapeutic option with antibiotics in 28 patients with confirmed diagnosis of MS.[23]

Biradar SV et al (2006), studied the comparative study of approaches used to improve solubility of roxithromycin, study deals with exploring the effect of homogenization, homogenization followed by freez drying and spray drying in the presence of solubilizers on drug solubility I dissolution rate.[24]

EI-Rabbat N et al (2006), studied A validated spectro fluorometric assay for the determination of certain macrolide antibiotic in pharmaceutical formulations and spiked biological fluids. The method is based on the condensation of 10% (w/v) Malonic acid and acetic acid anhydride under the catalytic effect of tertiary amine groups of the studied macrolides.[25]

Gao Y et al (2006) studied the preparation of roxithromycin – polymeric microspheres by the emulsion solvent diffusion method for taste masking, microspheres of roxithromycin with eudragit S 100 and silica were prepare, the effect of different polymers and drug polymer rations on taste masking and character of microsphere were quvestigated.[26]

Sun J et al (2006) studied the impact of pharmaceutical dosage forms on pharmacokinetic of roxithromycin in healthy human volunteers. The degradation kinetic and product of roxithromycin were investigated in simulated gastric fluid and simulated intestinal fluid.[27]

Suzuki M et al (2002) studied the inhibitory action of a macrolide antibiotic, roxithromycin, on co-simulator molecule expression *in vitro* and *in vivo*, result suggest that roxithromycin exerts its immune modulating effect through suppression of both cell activation and co-stimulatory molecule expressions induced by antigenic stimulation.[28]

Hopstaken RM et al (2002) studied is roxithromycin better than amoxicillin in the treatment of acute lower respiratory tract infections in primary care A double – blind randomized controlled trial. The surplus value of roxithromycin was riot confirmed. Amoxicillin remains a reliable first-choice Antibiotic in the treatment of LRTI.[29]

Akamatsu H et al (2001), studied the effects of roxithromycin on adhesion molecules expressed on endothelial cells of the dermal microvasculature using flow cyclometer at a concentration of 0.5mkg/m which is lower than the therapeutic plasma concentration.[30]

Kastner V et al (2001) reviewed that the influence of macrolide antibiotic on promotion of resistance in the oral flora of children. One week post treatment, up to 90% of children harbored macrolide – resistant strains in their oral flora.[31]

Zhong DF et al (2000), studied the identification of the metabolites of roxithromycin in humans. Metabolites of RXM in the bile of four chole cystictomy patients with t-Tube drainage and in the urine and plasma of four healthy volunteers after signal oral doses of 150 mg of RXM were investigated.[32]

Nakanura H et al (1999), reviewed that the clinical and immunoregulatory effects of roxithromycin therapy for chronic respiratory tract infection. Clinical parameters and neutrophil chemo tactic mediates in the epithelial living fluid of CLRTI patients were examined before and after 3 months oral administration of RXM.[33]

Moniot –ville N et al (1998), studied the acceptability, efficacy and safety of a new pediatric oral suspension of roxithromycin in respiratory tract infections in 210 children, aged between 2 and 8 years. A dose of 5-8 mg/kg/day roxithromycin was given orally for 5-10 days.[34]

Dietz A et al (1998), reviewed the severe adverse effect (churg-strass syndrome) after the intake of macrolides like azithromycin and roxithromycin, are increasingly preferred over erythromycin at the ear, nose and throat due to improved oral reabsorption, better penetration into tissue, prolong half life, extended antibacterial activity and better pharmacokinetics.[35]

Milne RJ et al (1997), studied the Tolerability of roxithromycin vs erythromycin in comparative clinical trials in patients with lower respiratory tract infections. Where stated 942 patients in 13 studies received erythromycin in various formulations and dosages. Most of the adverse events occur with erythromycin.[36]

Alhymayyd MS et al (1997), studied the pharmacokinetic interaction between erythromycin clarithromycin roxithromycin and phenytoin in rat. Animals were injected with phenytoin (100mg/kg) daily for 4 days and then were given phenytoin 20mg/kg alone or together with erythromycin 50mg/kg clarithromycin 50mg/kg roxithromycin 50mg/kg result suggest that the harmfully drug-drug interaction occur if phenytoin is administered with macrolides.[37]

Barreto DG et al (1996), studied the safety and efficacy of roxithromycin in patients with upper respiratory tract infection with the dose of 300mg once daily in 920 patients with acute pharyngo-amygdalitis of probable bacterial etiology. At the end of the treatment 92% of the 894 patients eligible for evaluation respond satisfactorily 6.5% showed improvement and remaining 15% unsatisfactory response.[38]

Gasser R et al (1996), studied the oral treatment of late lyne borreliosis with a combination of roxithromycin and co-trimoxazole in 18patients and result suggested were this combination has been successfully in order to thwart late lyme disease.[39]

Akamatru H et al (1996), reviewed the effect of roxithromycin on the generation of reactive oxygen species using human neutrophils and a cell-free xanthene – xanthenes oxidase system was examined.[40]

Shiral T et al (1995), studied the effect of 14 membered ring macrolide therapy on chromic respiratory tract infections and polymorph nuclear leukocyte activity oral administration of erythromycin (400 or 400mg) roxithromycin (150 or 300mg) or clarithromycin (200 or 400mg) given daily for at least 2 months was evaluated.[41]

Wenrmann T et al (1993), studied the Roxithromycin exert different effects on post prandial antroduodenal motor function and gastrointestinal symptoms in neatly subjects.[42]

Costa P et al (1992), studied the disposition of roxithromycin in the epididymis after repeated oral administration.[43]

Jehl F et al (1992), studied the penetration of roxithromycin into gingival tissue at steady state in 30 patients treated orally with 150 mg ever 12 hr for 5 days.[44]

Begue P et al (1995), reviewed the overall safety of roxithromycin in pediatric clinical-studies in a fetal of 477 children ,aged 2 month to 15 years, suffering from RTI or skin and tissue infection were treated with roxithromycin. The mean daily dose 6 mg/kg/day administered b.i.d. the overall safety of roxithromycin was assessed.[45]

CHAPTER 3

AIM AND PLAN OF WORK

3.1 Aim

As per the literatures, a suitable dosage form for paediatric patients will improve the compliance. Roxithromycin is an semi synthetic antibiotic effective against a broad spectrum of pathogens common in paediatric infection. The safety and pharmacokinetics of a b.i.d dose of Roxithromycin were studied in paediatric patients from 2 month to 15 years of age . the mean dose is 6 mg / kg /day administered will achieve therapeutic concentrations in children.[45]

Based on the above literatures the objective of the present study was focused to develop a stable oral suspension of suitable dose of Roxithromycin by masking the bitter taste to make it palatable for infants and children.

Although there are various technique to mask the bitterness of a drug, literatures had proven that the ion exchange resin could mask the bitterness due to amines.

Since roxithromycin produces bitterness due to amines present, the ion exchange resins was chosen a tool for the present study to mask bitter taste.

3.2 PLAN OF WORK

The scheme of the proposed study is as follows

- Methods
  - Pre formulation study of roxithromycin
  - Formulation of taste masked roxithromycin oral suspension
- Evaluation of formulated suspension
  - PH
  - Wt /ml
  - Viscosity
  - Sedimentation volume
  - Assay
  - Stability studies
  - Microbial limit test for the optimized formulation

CHAPTER 4

(Materials and Method)

4.1.Materials

4.1.1 Ingredient used

Materials	Supplier
Roxithromycin	Shasun chemicals and drugs,Ltd,Pondicherry.
Indion 204	Ion Exchange India ltd
Sugar	M.B. Sugar Mills,Maharastra
Methyl paraben	Salicylates ch. Pvt. Ltd,Hyderabad
Propyl paraben	Salicylates of chemicals pvt ltd,Hyderabad
Sorbitol	Deosen corporation Ltd – China
Veegum	Zacfa chemicals – Gujrat
Na Cmc	Hyundae fecs co. ltd.,Korea
Glycerin	Godrej industries Ltd,Mumbai
Na citrate	Sunil chemicals thane,Mumbai
Citric acid	Sunil chemical thane,Mumbai
Peppermint flavours	Lux flavour ,Chennai

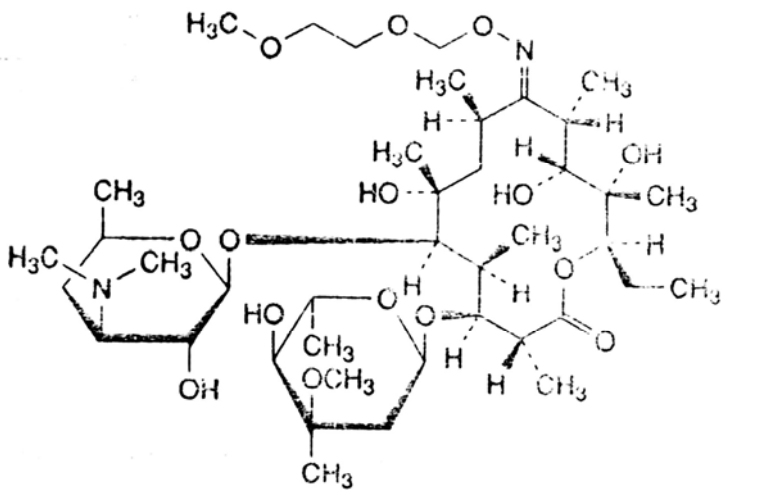
Colour	Roha dyechem, maharastra
MAG	Umang p'tech Pvt.Ltd,Chennai
Water	Madras Pharmaceuticals, Chennai

4.1.2 Equipments and Instruments used

S.No	**Instrument/Equipment**	**Supplier**
1	Hot plate	Remi Mumbai
2	Shimadzu Ax zoo Digital Balance	Shimadzu Japan
3	Crest sonicator	Electro lab, Chennai
4	Magnetic stirrer	Electro lab, Chennai
5	Emulsifier	Electro lab, Chennai
6	Homogenizer	Bectoehem – Hyderabad
7	Colloidal mill	Bectoehem – Hyderabad
8	pH meter	ELCO –Mumbai
9	UV spectrometer	Shimadzu,Japan.

4.1.3 Drug Profile

Roxithromycin:[45, 46]



Category :-

Anti Bacterial

Mol. formula and Wt.:-

$C_{41}H_{76}N_2O_{15}$, 837.

Definition:-

(3R,4S,5S,6R,7R,9R,1) S,12R,13S,14R)-4[(2,6 Dideoxy -3 – C-Methyl-3-O-methyl-∝-1-ribo-hexopyranosyl)-14-ethyl-7,12,13-trihydroxy-10-[(E)-[(2-methoxyethoxy]imino)-3,5,7,9,11,13-hexamethyl-6-[(3,4,6-trideoxy-3-(dimethylamino)-β--d-xylo-hexobyranosyl)oxy] oxacyclotetradecan-2-one.

Content:-

96.0 percent to 102.0 percent (Anhydrous substance)

Description:-

Crystalline powder

White in colour

Solubility:-

Very slightly soluble in water, freely soluble in Acetone, in alcohol and in methylene chloride. It is slightly soluble in dil.Hcl.it shows polymorphism.

Antimicrobial Action:-

It is more active than erythromycin. It inhibit protein synthesis.

Pharmacokinetics:-

Following oral administration roxithromycin is absorbed, with a bioavaibility of about 50% peak plasma concentrations of about 6 to 8 µg / ml occurred around 2 hours after a single dose of 150mg. The mean peak plasma concentration of steady state after a dose of 150mg twice daily is 9.3 µg / ml. Absorption is reduced when taken after, but not before, a meal. It is widely distributed in tissue and body fluids. It is reported to be about 96% bound to plasma protein (mainly α1 – acid glycoprotein) at through and only about 86% is bound at usual peak

concentrations. Small amount of roxithromycin are metabolized in liver, and the majority of the dose is excreted in the faeces as unchanged drug and metabolites; about 7 to 12% is excreted in urine, and up to 15% via lungs.

Adverse effects and precaution:-

Gastrointetestinal disturbances are the most frequent adverse effect, but are less frequent than with erythromycin. Increases in liver enzyme values and hepatitis have been reported. Rashes and other hypersensitivity reaction, headache, dizziness, weakness and changes in blood cell counts have also occurred.

Effect on pancreas:-

Acute pancreatitis, with duodenal inflammation, pain pancreatic enlargement and raised serum – amylase developed within 24hr. of substitution of roxithromycin for erythromycin ethyl succinate in a patient being treated for respiratory tract infection.

Uses and Administration:-

Roxithromycin is a macrolide antibiotic with actions and uses similar to those of erythromycin like as urinary tract infection, respiratory tract infection, asthma. It is given by mouth in a doses of 150 mg twice daily or sometimes 300mg once daily, before meals, in the treatment of susceptible infections.

4.1.4 Excipients Profile

(A) Sorbitol [47]

Non Proprietory Names:-

USPNF – Sorbitol

IP – D-Sorbitol

BP – Sorbitol

Synonyms:-

C*Pharamasorbidex: E420; 1,2,3,4,5,

6 – Hexane Hexol; liponic 76 NC; Meritol;

Neosorb ; Sorbite; D- Sorbitol

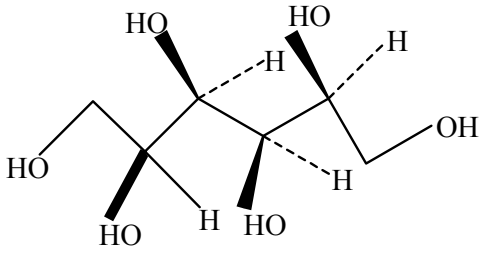
Chemical Name and CAS Registry No:-

D-Glucitol [50-70-4]

Empirical formula and mol.wt:-

$C_6H_{14}O_6$, 182.17

Structural Formula:-



Functional Category:-

Humectants; Plasticizer, Sweetning Agent, Tablet and Capsule diluent.

Application in Pharmaceutical formulation:-

It is used as diluents in tab formula. It is particularly used in chewable tablet owing to its pleasant, sweet taste and cooling sensation.

In capsule – plasticizer

(B-) Veegum "(Magnesium Aluminum Silicate)"

Non Proprietary Name:-

BP – Al.Mg. Silicate

Synonyms:-

Aluminosilic acid, Mg. salt, Carrisorb, Gelsorb, Mg. Al. Silicate etc.

Chemical Name of CAS Registry no:-

Al. Mg. Silicate:- [12511-31-8]

Mg. Al. Silicate:- [1327-43-1]

Empirical formula and Mol. Wt:-

It is a polymeric form of Magnesium., Aluminium, Silicon and oxygen and water. Average Chemical Analysis is expressed as oxides

Silicon dioxide:- 61.1%

Mg.oxide:- 13.7%

Al.oxide: 9.3%

Titanium oxide:- 0.1%

Ferric oxide:- 2.9%

Ca oxide:- 2.7%

Structure:-

Composed of a three – lattice layer of octahedral alumina two tetrahedral silica sheets. The aluminium substituted to varying degrees by magnesium additional elevate include – iron, lithium, titanium, calcium and carbon.

Category:-

Adsorbent, stabilizing agent, suspending agent, viscosity increasing agent.

Application in pharmaceutical formula:-

It is used in tablet, ointments, creams in oral suspension. It is used as suspending agent alone or in combination.

Stabilizer, disintegrating Agent etc.

Description:-

Off-white to creamy white, odourless, tasteless, soft, slippery small flakes or fine powder.

Typical property:-

2.418 gm/ cm^3 – Density

6 – 9.98% - Moisture Content

Solubility – Practical insoluble in alcohol, water and organic solvents.

Stability and storage condition:-

It is stable in dry condition and a wide range of pH, has base – exchange capacity and compatible with organic solvents. It is stored in well closed container and stored in cool dry place.

Incompatibility:-

It is generally unstable in acidic solution below pH 3.5. it is as with other clays, may absorb some other drugs. this can result in low bioavailability. If the drug is tightly bound or slowly desorbed e.g amphetamine sulfate, tolbutamide ,diazepam etc.

(C) Na-CMC

Non-Proprietary Name:-

IP & BP- Carmellose sodium

USP – Carboxymethyl cellulose sodium.

Synonym:-

Cellulose gum, sod cellulose glucolate.

Chemical name and CAS Registry no:-

Cellulose, Carboxymethyl ether, sodium salt (9004-32-4)

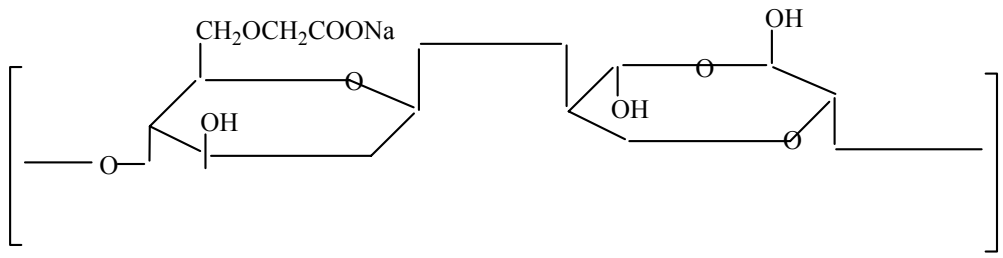
Empirical formula and Mol.wt:-

USP describes its sod salt of a poly carboxy methyl ether of cellulose.

Mol.wt.:-

9000 – 70,000

Structure:-



Category:-

Coating Agent, Stabilizing Agent, Suspending Agent, Tablet and Capsule disintegrator, tablet binder, viscosity increasing Agent, Water Absorbing Agent.

Application:-

It is used as a suspending agent, binding agent and as a base for gels and pastes.

Description:-

White to almost white, odourless, granular powder.

Typical Property:-

Density (Bulk) – 0.52g/cm^3

(Tapped) – 0.78g/cm^3

pKa – 4.30

M.P –becomes Browns at approximately 227^0c and chars at 252^0'c.

Moisture content:-

Typically contain less than 10%water however it is hygroscopic and absorb significant amount of water at a temperature up37^0c to at relative humidity of about 80%.

Solubility:-

Practically insoluble in acetone, ether, toluene, and ethanol (95%) easily dispersed in water.

Viscosity:-

Viscosity		Grade
10-15	–	Akucell Af0305 – Low viscosity
1500 – 2500	–	Akucell Af 2785 – high viscosity
8000 – 12,000	–	Akucell Af 3085 – Medium viscosity

Stability and storage:-

It is stable though hygroscopic material. Under high humidity condition. Its absorption high amount of water (>50%). Aqueous solution stable at pH 2-10 below pH 2 solution precipitate and put 10-viscosity decreased. It is sterilized at dry state at 160^0c for 1hr. Sterilization by gamaradiation also reduce its viscosity.

Antimicrobial preservatives added for prolong stores it is stored in well closed container in cool, dry place.

Incompatibility:-

Incompatible with strong acidic solution and with the soluble salts of iron and some other metals eg-Aluminium, Mercury, iron and zinc. Precipitate occur with ethanol (95%) and precipitation occurs at ph<2. It form's complex coacervates with pectin and gelatin.

Safety:-

It is non toxic and non irritant material oral consumption of large amount of carboxy methyl cellulose sodium have a laxative effect. The WHO has not specified an acceptable daily intake for sod cmc as a food additives.

LD(50) (Guinea pig, oral) – 16g/kg

LD 50 (rat, oral) – 27g/kg

(d) Glycerin

Non proprietary name :- BP – Glycerol

IP – Concentrate Glycerin

USP – Glycerin

Synonyms:-

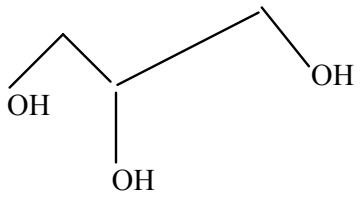
Glycon G – 100; 1,2,3 – Propentriol; trihydrooxy propane glycerol.

Chemical name and CAS Registory No:-

Propane – 1,2,3 – triol (56 – 81 – 5)

Empirical formula and Mol.Wt. – $c_3 11_8 0_3$ 92.09

Structure:-



Category:

Antimicrobial preservative, emollient, humectants, Plasticizer, Solvents, Sweetening Agent, tonicity agent.

Application:

It is used in Pharmaceutical formulation. It is used as a antimicrobial preservative for the protection to microbial growth and it is used as emollient, humectants. It is used as a plasticizer in formulation and act as a solvent and sometimes it is used as a sweetning agent also.

Description:

Clear, colourless, viscous, hygroscopic liquid, sweet taste.

Typical property:

Boiling point – 290^{o}c

Density – 1.2656g/cm^3 at 15^{o}c

1.2638g/cm^3 at 20^{o}c

1.2620g/cm^3 at 25^{o}c

Freezing point – 10% solution (-1.6^{0}c)

Melting point – 17.8^{o}c

Osmolarity – a 2.6% r/v aq/solution is osmotic with serum.

Solubility:

Acetone – slightly soluble

Benzene – practically insoluble

Chloroform – practically insoluble

Ethanol (95%) – soluble

Ether – 1 in 500

Water – soluble

Surface tension – 63.4 (dynes/cm) at 20^{o}c

Viscosity:

Concentration of.Aqueous solution of glycerin – Viscosity at 20^{o}c

5 – 1.143

10 – 1.311

25 – 2.095

50 – 6.05

60 – 10.96

Stability and storage condition:

It is decomposes on heating with the evolution of toxin acrolein. Mixture of glycerin with water, ethanol, propylene glycol is stable. When stored at low temperature it crystalline and not melt until warmed upto 20^{o}c. it is stored in airtight container in a cool, dry place.

Incompatibility:

It may explode when mixed with strong oxidizing agent such as chromium trioxide, potassium chlorate. Black discolouration occur in the presence of light or an contact with zinc oxide or basic bismuth.

Safety:

Large dose may produce headache, thirst, nausea and hyperglycemia.

The therapeutic paranteral Administration of very large dose of glycerin may induce renal failure, hemolytic, hemoglobinuria.

(E) Na – Citrate

Non Proprietary Name:

BP – Sod citrate

Ph EV – Natril citras

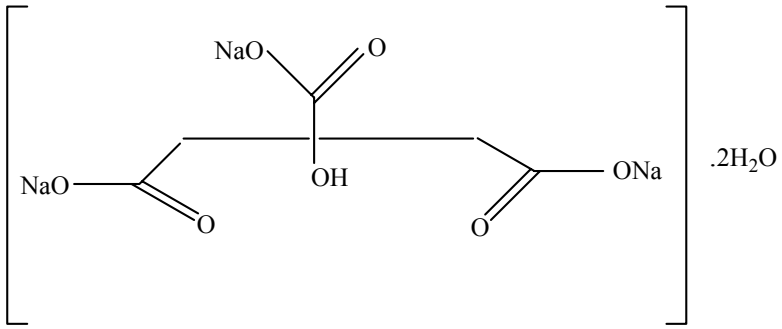
Synonyms:

Citric acid trisodium salt; E 331; sodium citrate tertiary; trisodium citrate.

Empirical formula and Mol.Wt:

$C_6H_5Na_3O_72H_20$ 294.10

Structure:



Category:

Alkalizing Agent, Buffering Agent, emulsifier, sequestering Agent.

Application:

It is used in pharmaceutical formulation as a Alkalizing Agent and maintain the pH as a buffering Agent. It is used as a emulsifier and sequestering agent also.

Description:

It consist of odourless, colourless, monoclinic crystals or white crystalline powder with a cooling saline taste. It is slightly deliquescent in moist air and in warm dry air it is efflorescent.

Typical property:

Acidity / Alkalinity: pH – 7-9 (5% w/v aq.solution)

Density (bulk) 1.12g/cm^3

Density (Tapped) 0.99 g/cm^3

Density (True) – 1.19g/cm^3.

Melting point:

Converts to the anhydrous forms at 150^{o}c

Osmolarity:

3.02% w/v aq.soln in iso-osmotic with serum

Particle size distribution:

Various size are available.

Solubility:

Soluble 1 in 1.5 of water, 1 in 0.6 of boiling water, practically insoluble in ethanol (95%).

Stability and storage condition:

It is stable material Aqueous solution may be sterilized by Autoclaving on storage aq.soln may cause the separation of small, solid particles from glass container.

Bulk material should be stored in airtight container in cool dry place.

Incompatibility:

It is slightly Alkaline and its salts may be precipitated from their Aqueous or hydro alcohol solution.

Calcium and strontium salts will cause precipitation of the corresponding citrates. Other incompatibility includes bases, reducing agent, oxidizing agents.

Safety:

After ingestion, sodium citrate is Absorbed and metabolized to bicarbonate. It is nontoxic and non-irritant excipients, excessive consumption may cause gastro intestinal discomfort or diarrohea.

(F) Citric Acid

Non proprietary name:

BP – Citric acid monohydrate

IP – Citric acid

Synonym:

2 – hydroxy – 1,2,3 – Propantricarboxylic acid monohydrate.

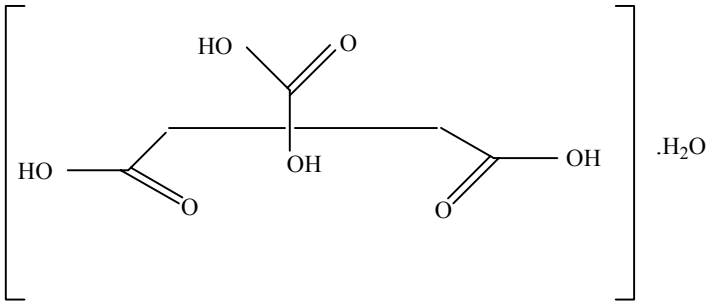
Ch.name and CAS Registry No:

2 – hydroxy – 1,2,3 – Propantricarboxylic acid monohydrate (5943 – 29 -1)

Empirical formula and mol.wt:

$C_6H_80_7H_20$ (210.14)

Structure:



Category:

Acidifying agent, antioxidant, buffering Agent, Chelating Agent, Flavour enhancer.

Application:

It is used as Acidifying Agent and it is also used as Antioxidant to prevent product from oxidation. It is used as buffering agent and complexing Agent also.

Description:

Colorless or translucent crystals, or as a white crystalline, efflorescent powder. Odourless and strong Acidic taste. Crystal structure is orthorhombic.

Typical Property:

Acidity / Alkalinity : PH – 2.2 (1%w/v aqueous solution)

pka_1 – 3.128 at 25^0c

pka_2 – 4.761 at 25^0c

pka_3 – 6.396 at 25^0c

Density – 1.542g/cm^3

Hygroscopicity:

At pH less than about 65%. At pH below 65-75% citric acid monohydrate absorb insignificant amount of moisture but under more humid condition substantial amount of water are absorbed.

Melting point:

100^0c (soften at 75^0c)

Solubility:

Soluble 1 in 1.5 parts of ethanol and 1 in less than 1 part of water. Sparingly soluble in ether.

Stability and storage condition:

It loses water of crystallization in dry air or when heated to about 40^0c. it is slightly deliquescent in moist air. Dilute aqueous solution may ferment on standing.

Bulk citric acid stored in airtight container in cool, dry place.

(G) Methyl Paraben

Synonyms:

E 218; 4-hydroxybenzoic acid methyl ester; methyl ester; methyl P-hydroxy benzoate.

Chemical Name and CAS No:

Methyl 4-hydroxybenzoate

(99-76-3)

Empirical formula:

$C_8H_80_3$

Molecular wt.:

152.15

Category:

Antimicrobial preservative.

Description:

Methyl paraben crystalline powder. It is odourless or almost colourless and has slight burning taste.

Typical properties:

Antimicrobial Activity: Exhibit Antimicrobial activity between PH 4-8.

Density (True) : 1.352g/cm^3

Solubility :

Soluble in various solvents like ethanol, ethanol 95%, ethanol 50%, ether, glycerin, mineral oil, peanut oil, propylene glycol and water in different proportionate.

Incompatibility:

The Antimicrobial activity of methyl paraben and other paraben is considerably reduced in the presence of non ionic surfactants, such as polysorbate 80, as a result of miscellization. Incompatibilities with other substances such as betonite, magnesium trisilicate, talc, tragacanth, sodium alginate, essential oils, sorbitol and atropine have been reported.

Safety:

Parabens are non mutagenic, non teratogenic and non carcinogenic.

Stability and storage:

Aqueous solution at pH 3-6 are stable for upto 4 years at room temperature. While at pH 8 it undergoes rapid hydrolysis methylparaben should be stored in well-closed container in a cool dry, place.

(H) Propyl Paraben

Synonym:

H-Hydroxybenzoic acid propylester; p – hydroxybenzoate.

Chemical name and CAS no:

Propyl 4-hydroxybenzoate (94-13-3)

Empirical formula:

$C_{10}H_{12}0_3$

Molecular wt.:

180.20

Category:

Antimicrobial preservative.

Description:

It occurs as white, crystalline, colorless and tasteless powder.

Incompability:

The Antimicrobial activity of methyl paraben and other parabens is considerably reduced in the presence of nonionic surfactants, as a result of micellization.

Safety:

Propyl paraben and other parabens are widely used as antimicrobial preservatives in cosmetics, food products and oral formulations. Due to the irritant potential of the parabens now they are regarded as being unsuitable for injections and ophthalmic preparations.

Stability and storage:

Aqueous solutions at pH 3-6 are stable for up to 4 years at room temperature while at pH 8 it undergoes rapidly hydrolysis. Methyl paraben should be stored in well closed container in a cool dry place.

(I) Sugar (Sucrose)

Synonyms:

Best sugar, Cane sugar, Refined sugar, Saccharose, Sugar etc.

Chemical name and CAS No:

β-D-Fructofuranosyl - ∝-D-glucopyranoside. (57-50-1)

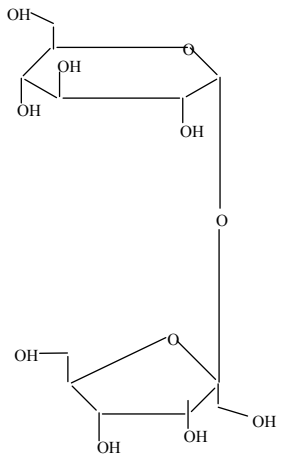
Empirical formula:

$C_{12}H_{22}0_{11}$

Molecular wt.:

342.30

Structure:



Category:

Coating Agent, Granulating Agent, Sugar coating Adjunct, Suspending Agent, Sweetning Agent, Tablet binder, Tablet filler, Viscosity increasing Agent.

Description:

Colorless crystals, as crystalline masses or blocks, or as a white crystalline powder odorless and sweet taste.

Typical property:

Density (Bulk) – 0.93g/cm_3 (Crystalline sucrose)

- 0.60g/cm_3 (Powder sucrose)

pka = 12.62

Solubility:

Crystalline free flowing where as powder sucrose is a cohesive solid.

Melting point – 160-126^{0}c

Moisture content – Finally divided sucrose is hygroscopic and absorb upto 1% water.

Osmolarity:

A 3.25% w/v aqueous solution is iso osmotic with serum.

Solubility:

Chloroform – Practically insoluble

Ethanol – 1 in 400

Water – 1 in 0.2 at 100^{0}c

Propane 2 – 1 in 400

Specific gravity:

At 2% sucrose solution – 1.0060

At 6% sucrose solution – 1.0219

10% sucrose solution – 1.0381

20% sucrose solution – 1.0810

50% sucrose solution – 1.2296

Stability:

It has good stability at room and at moderate pH it Absorb 1% moisture which is realized at temperature increasing 90^0c at 160^0c it caramelizes at dilute solution liable to fermentation by microorganism but increases concentration resist decomposition aqueous solution sterilized by Autoclaving or filtration. Bulk material stored in well closed container in cool and dry place.

Incompability:

It is powder form contaminated lead to incompatibility with active ingredient. Example – Ascorbic acid is also contaminated by sulfite from refining process.

Sucrose may attack aluminum closure.

Safety:

Sucrose is hydrolyzed in small intestine by sucrose enzyme in to fructose and dextrose and then Absorbed.

It is widely considered to be more carcinogenic than other carbohydrate. Since it is more easily connected to dental plaque. For this reason, its use in oral formulation is declining.

It is also associated with obesity, renal damage, and a no.of other disease.

L D (50) (mouse) IP – 14g/kg

L D (50) ,rat (oral) – 29.7g/kg

(J) Indion 204[48] *(http://www.ionindia.com)*

Indion 204 is based on a cross linked polyacrylic matrix. It is a high purity grade weak acid cation exchange resin.

Description:

White to pale cream colored powder, free from foreign matter.

Typical property:

Particle size distribution

Retain on 100# : 1%

200#: 45%

Solubility:

Insoluble in water and in common solvents.

Functional group:

Carboxylic acid

Moisture content: 5%

Ion Exchange capacity : 10millieq/g

Toxicity :

Indion 204 is a high molecular weight cross – linked polymer and hence not absorbed by body tissue.

Stability and storage:

It is hygroscopic in nature and hence should be stored in an airtight container.

The theoretical quality of drug, which can be complexed with resins, depends upon two factors, viz.

1. The exchange capacity of resin
2. The equivalent weight of the drug

Generally for the drugs having a molecular weight between 300 and 500, the required drug resin is 1:2.25, while for the drug have high molecular weight less than 600, the required drug resin ratio is 1:4.

Application:

- ❖ Taste making
- ❖ Sustained release
- ❖ Vit. B12 stabilizing
- ❖ Tablet disintegrate

Chapter 5

5.1 Method

5.1.1 Preformulation[49]

Preformulation is the first step in the rational development of dosage form of a drug substance and it is defined as investigation of physical chemical properties of a drug substance alone and when combined with excipients.

5.1.2 Compatibility study[50]

Compatibility studies are done to find our whether there is any interaction between drug and excipients. The drug is mixed with the excipients in the ratio 1:1 and 1:5 and observations were noted.

Inference:

Observations were concluded that, the excipients selected for formulation of Roxithromycin suspensions.

Accelerated conditions:

This study is done by inducing a stress at different temperature. The rate of the reaction increases of the temperature.

I - 40^0c; pH – 75%

II - 25^0c; pH – 60%

III - Room temperature

The drug is mixed with the excipients in the ratio 1:1 and are subjected to different temperature. The study was done for one week and the observations are given in the table.

5.1.3 Preformulation study of Roxithromycin[49]

Table No 3

1	Appearance	white or crystalline powder
2	Solubility	Very slightly soluble in water, freely soluble in acetone, in alcohol and in methylene chloride. It is slightly soluble in dilute Hcl acid.
3	Identification	
	A) Sp.optical Rotation	-93 to -96
	B) By IR	Sample Peak size and retention time same as reference solution.
4	pH	Its pH was tested by 10% w/v solution of Roxithromycin and the value is 4.5.
5	Content	96 to 102 percent (Anhydrous sub)
6	Heavy metals	Maximum 10PPM
7	Related substance (By liquid chromatography)	0.05
8	Water	Maximum 3%, on 0.200g
9	Sulphated Ash	Maximum 0.1%, determined on 1.0g
10	Assay	P – cymene : 0.8% to 2.5% Camphor : 5% to 15% Borneol : 1.5% to 5% ∝-terpeneol : 1% to 2.6%

5.1.4. INFRARED SPECTROSCOPY

By using FTIR technique Roxithromycin and polymers like, sodium carboxy methyl cellulose and Roxithromycin optimum formulation were identified.

The interpretation are shown in following tables

TABLE NO.4

IR SPECTRA DATA [POTASSIUM BROMIDE PELLETS]

FOR PURE ROXITHROMYCIN

Frequency cm^{-1}	Groups Assigned
3464	O – H stretching
2980	C – H stretching
1728	C = O stretching
1172	C – O stretching
1077	C – O stretching
1012	C – O stretching

TABLE NO.5

IR SPECTRA DATA [POTASSIUM BROMIDE PELLETS]

FOR PURE SODIUM CARBOXY METHYL CELLULOSE

Frequency cm^{-1}	Groups Assigned
3448	O – H stretching
2925	C – H stretching

1618	C = O stretching
1422	C – H stretching
1059	C – O stretching

TABLE NO.6

IR SPECTRA DATA [POTASSIUM BROMIDE PELLETS]

FOR OPTIMUM ROXITHROMYCIN

FORMULATION(RXS06)

Frequency cm^{-1}	Groups Assigned
3464	O – H stretching
2979	C – H stretching
1730	C = O stretching
1171	C – O stretching
1077	C – O stretching
1012	C – O stretching

REPORT

The spectrum was interpreted and identified as , Roxithromycin , and sodium carboxy methyl cellulose. The presence of excipients such as sodium carboxymethyl cellulose along with the drug does not cause any interaction.

5.2 Compatibility study of Roxithromycin with Excipients

Table no.7

Drug	Excipients	Ratio	Physical Observation								
			First day			Fourth day			After one weak		
			RT	25^{O}C	40^{O}C	RT	25^{O}C	40^{O}C	RT	25^{O}C	40^{O}C
R	Indion 204	1:1	ND	ND	ND	ND	ND	ND	ND	ND	ND
R	Methyl Paraben	1:1	ND	ND	ND	ND	ND	ND	ND	ND	ND
R	Propyl paraben	1:1	ND	ND	ND	ND	ND	ND	ND	ND	ND
R	Sorbitol	1:1	ND	ND	ND	ND	ND	ND	ND	ND	ND
R	Veegum	1:1	ND	ND	ND	ND	ND	ND	ND	ND	ND
R	Na CMC	1:1	ND	ND	ND	ND	ND	ND	ND	ND	ND
R	Na Citrate	1:1	ND	ND	ND	ND	ND	ND	ND	ND	ND
R	Citric acid	1:1	ND	ND	ND	ND	ND	ND	ND	ND	ND

R – Roxithromycin **ND – Non detectable** **RT-Room temperature**

5.3 Formulation trials for Roxithromycin suspension

Batch Size : 1000ml

Table No:-8

S.No	Ingredients	UOM	Rxso1	Rxso2	Rxso3	Rxso4	Rxso5	Rxso6
	Roxithromycin	g	11	11	11	11	11	11
	Indian 204	g	-	40	35	35	35	35
	Sugar	g	-	500	500	500	500	500
	Methyl paraben	g	1.8	1.8	1.8	1.8	1.8	1.8
	Propyl paraben	g	0.2	0.2	0.2	0.2	0.2	0.2
	Sorbitol	g	60	-	-	-	60	60
	Veegum	g	3	3	3	3	-	-
	Na cmc	g	-	-	2	2	2	2
	Glycerin	g	30	30	-	-	-	30
	Na Citrate	g	3	3	3	6	6	6
	Citric acid	g	0.5	0.5	0.5	1	1	1
	Aspartame	g	1	1	-	-	-	-
	Pipermint flavor	g	5	5	5	5	5	5
	Colour (senset yellow)	g	0.044	0.044	0.044	0.044	0.044	0.044
	Mono Ammonium glycyrizinate	g	5	5	5	-	-	-
	Water	L	9.5	9.5	9.5	9.5	9.5	9.5

5.4 Manufacturing Process

PREPARATION OF SUSPENSION

STEP 1

Transferred 120ml deionized water in to a cleaned stainless steel vessels disperse slowly under stirring 35gm of resin stir for 15min. Add slowly under stirring 11gm of Roxithromycin into the tank continue stirring for further ½ hour. During the stirring process close the tank with S.S. lid.

STEP 2

Transfer 300 ml of deionised water in a suitable jacketed S.S.Vessels. Boil the water and add methyl and propyl paraben in to it also add sugar into it under stirring continue heating the solution till the temperature of the syrup attains 120^{o}c ensure the complete dissolution of the sugar. Continue stirring during this process. Discontinue heating add sorbitol in to sugar syrup continue stirring for sometime, till the temperature comes down to approximately 80^{0}c filter the hot sugar syrup through muslin cloth and transfer the same into the tank from step 1. Continue stirring after addition of sugar syrup.

STEP 3

Transfer 15gm of glycerin into a cleaned S.S. vessel and under stirring sodium CMC uniform suspension achieved. Transfer this to the manufacturing tank in step 1 continue stirring after addition.

STEP 4

Transfer 15gm glycerin in to cleaned S.S tank and add 5gm (MAG) mono ammonium glycerrhzinate under stirring and dissolve completely in glycerin transfer this in to step 1.

STEP 5

Transfer 10ml deionised water in to S.S. vessel and add sodium citrate 6gm stir till it dissolve. Add citric acid and stirr till it dissolves. Transfer it in to step 1. Transfer 2ml water in vessels add sunset yellow supra colour and stir till it dissolve. Transfer same into the ufg tank and the transfer the pippermint flavor in to a S.S vessel and then it transfer in to step 1.

STEP 6

Check pH adjust to 4.5 with either dilute with NaoH or Hcl. Stir continue make the volume upto 1 liter and stir for 15 minute. Stop stirring close the tank with suitable lid.

5.5 PARAMETER EVALUATED FOR ORAL SUSPENSION[51]

The parameters evaluated for oral suspension are as follows weight per ml, pH Viscosity ,percentage sedimentation volume, Assay, Antimicrobial studies.

5.5.1 Appearance:

The appearance in a graduated glass cylinder or transparent glass container is noted.

5.5.2 Color, odor, and Taste:-

These characteristic are specially important in orally administered suspensions. Variation in colour often indicates poor distribution and differences in particle size. Change in colour, odour and taste can also indicate chemical instability

5.5.3 Weight per ml:-

A Pre weighed 25 ml volumetric flask was taken and the oral suspension was added up to the mark. The net volume is noted. Then weighed the above volumetric flask to evaluate weight per ml.

5.5.4: pH:-

It is an Important parameter, which reflects the stability of suspension. Any change in pH indicates the degradation of drug or other ingredients. For stabilizing the suspension the pH has to be maintained by the addition of buffer. The pH was checked initially and the after 15 days. This was measured by pH meter

5.5.5 Viscosity:-

It is the measure of the internal friction of a fluid. It is a rheological consideration, which indicates the setting of dispersed particles and change in. flow property of the suspension, when container is shaked and when the product is dispensed from the bottle Brookfield viscometer in a std. condition was used to measure it. here viscosity was measured for all formulations in standard condition.

5.5.6 Particle size measurement:-

Particle size measurement permits evaluation of aggregation of crystal growth any change in particle size affects the sedimentation rate, care of redispersebility, making and efficacy properties of a disperse system.

The various methods used for the determination of average particle size, they are,

- Microscopic Technique.
- Sieving Technique.
- Sedimentation technique
- Coulter counter method.

5.5.7 Percentage sedimentation volume:

Sedimentation volume is important to measure since it affects the stability of suspension. Here the sedimentation volume was measured in percentage for determining sedimentation volume, the suspension was poured in to 100 ml

uniform. Graduated stopped cylinder and stored at room temp. [RT] without any external disturbances. The percentage volume of sediment formed was measured initially and after four weeks.

F = HU/HO x 100

Where

HU = Ultimate settled height of sediment

HO = Original height of sediment and

F = The percentage sediment volume.

5.5.8 Assay of Roxithromycin suspension:-

Solvent preparation:-

Take 125 ml of absolute ethane in 250 ml volumetric flask add 10 ml of conc. Hydrochloric acid and make up to mark with distilled water.

Reagent preparation:-

Weight 200 mg of 4 – diethyl amino benzaldehyde in 10 ml volumetric flask, dissolve in absolute ethanol. Add 0.1 ml of conc. Hydrochloric acid and make up to the mark with absolute ethanol.

Standard preparation:-

Weigh accurately 50 mg of Roxithromycin working standard in 25 ml volumetric flask dissolve in glacial acetic acid and make up to the mark with glacial acetic acid. Pipette 5 ml of the standard preparation in to 25 ml volumetric flask, add 1 ml of reagent, shake well and keep in boiling water bath for 30 min. among with sample preparation.

Sample preparation:-

Weight accurately suspension equivalent to 100 mg of Roxithromycin from a well – shaken bottle, in a 100 ml volumetric flask. Add 10 ml of solvent shake the flask. Add the solvent up to the mark and keep in sonicator bath for 1 hr. filter through whatman no. 41. Pipette 25 ml of the filtrate and transfer it to 100 ml separating funnel. Add 2 ml of strong ammonia solution and extract with 20 + 10 + 10 ml of chloroform. Collect 50 ml of the chloroform layer in 50 ml volumetric flask and make up to the mark with chloroform if necessary. Add 0.5 gm of sodium chloride to it and shake for a while. Evaporate 20 ml of chloroform layer in 25 ml volumetric flask on water bath taking care to avoid expulsion of chloroform from the volumetric flask during evaporation. Add 5 ml of glacial acetic acid shake well add 1 ml of reagent shake well and keep on boiling water for 30 min to develop a colour. After 30minute make up to mark with glacial acetic acid. Read the colour at 690nm against absolute ethanol as a blank preparation simultaneously using 5.0ml of glacial acetic acid, instead of sample and treating in a similar manner as done for standard and sample preparation from the Absorbance of standard and sample preparation calculate the content of Roxithromycin in each 5 ml of suspension.

Calculation:-

$$\frac{sample\,Abs.}{Std.Abs.} X \frac{Std.wt.}{25} X \frac{5}{25} X \frac{100}{spl.wt} X \frac{50}{25} X \frac{25}{25} X \frac{std\ purity}{100} X\ 5\ Xwt/ml$$

5.5.9 Stability studies:-

The most common form of physical instability occurring in suspensions is the setting out of the solid phase with the formation of sediment which is difficult to re-disperse on shaking

Crystal growth is also a cause of physical deterioration in some suspensions. Acceleration of crystal growth may be achieved by simulating the temperature fluctuations occurring under normal stage conditions, but at greatly increased frequency.

An ideal form apart from other dosage requirement should provide consistency of drug content and release through out its shelf life. The formulated taste masked roxithromycin oral suspension was packed in 50 ml amber coloured glass bottles and stored at a temperature of $40^{o}C \pm 2^{o}C$ and RH $75^{o}C \pm 5\%$ and a temperature. The product were stored for a period of 60days in the above mentioned conditions. The induct was analyzed at initial, 30 days and 60 days of storage.

After the storage period the formulation were evaluated for the following:

- Appearance
- Wt/ml
- pH
- Viscosity

- Particle sedimentation volume.
- Assay

5.5.10: Microbial limit test for the optimized formulation:

The product was subjected Total Bacterial count (TBC), Total fungal count (TFC) and for specified microorganism Escherichia coli.

Methods:-

TBC(Total Bacteria Count):-

Add 1 ml of pretreated sample to sterile Petridish and pour about 20 ml of sterile nutrient agar medium in to the plate and mix well by rotating in clock wise and anti clock wise direction.

2 plates are incubate at 35 ^{o}C-37 ^{o}C for 48 hrs. After incubation count the number of colony forming units and express the result as average for the 2 plates in terms of the number of colonies per ml

TFC(Total fungal count):-

Proceed as per the procedure described in the test for bacteria but use potato dextrose agar medium in place of nutrient agar and incubate the plates at 20 ^{o}C - 25 ^{o}C for 5 days.

For specified microorganism (E. coli):

The test was carried out as per the official method with the limitation only to primary test, in which 1.0 ml of sample was added to a tube containing 5

ml of macconkey broth and was incubated at 36 ^{o}C to 38 ^{o}C for 48 hrs and the result were interpreted.

CHAPTER – 6

Result and Discussion

6.1 Evaluation of Roxithromycin oral suspension

Based on the objective and plan of work, after preliminary studies six trial formulations of Roxithromycin oral suspension were formulated. The formulated trial batches were designed as Rxs01, Rx s02, Rxs03, Rxs04, Rxs05, and Rxs06.

All trial formulation were evaluated by selected parameter study. There parameter studies were (i) Evaluation of oral suspension and (ii) stability studies.

6.1.1 Parameter Evaluated for oral suspension

The import-out parameter evaluated includes pH, weight per ml, viscosity, particle size determination, percentage sedimentation volume, assay, microbiological analysis.

6.1.2 pH:-

The pH of oral suspension was checked since it indicates the stability of the drug. This parameter was evaluated initially and at 15 days. The observed mean values for all six trial batches are given table no.6. The observed data showed no deviation in pH for all six trial batches. The pH value ranged from 4 to 5.

pH values observed initially and after 15 days.

Table no.9

Formulations	pH values initially	pH values after 15 days
RxS01	4.91	4.87
RxS02	4.12	5.19
RxS03	4.92	5.02
RxS04	5.07	5.11
RxS05	4.81	4.93
RxS06	4.51	4.56

6.1.3 Weigh Per ml:-

Weight per ml of the oral suspension was checked for all six trail batches. The weight per ml of the six trial between 1.21 to 1.24. The details data given in

Table no. 10

S.No.	Formulations	Weight Per ml (initially)	Weight per ml (After 15 days)
1	RxS01	1.24	1.24
2	RxS02	1.23	1.22
3	RxS03	1.23	1.24
4	RxS04	1.21	1.21
5	RxS05	1.24	1.23
6	RxS06	1.22	1.22

6.1.4 Viscosity: The viscosity of six trial batches of oral suspensions was checked. Non-Newtonian fluids do not show a characteristic viscosity over a range of test conditions. Only an apparent viscosity can be measured, and its values depends on the conditions must be standardized with regard to the extent of premixing of the sample prior to the test, temperature, instrument speed and the spindle used. The observed data detailed given in table no.11

Table no. 11

S.No.	Formulations	Viscosity (initially CPS)	After 15 days(CPS)
1	RxS01	480	488
2	RxS02	490	498
3	RxS03	468	475
4	RxS04	370	379
5	RxS05	390	372

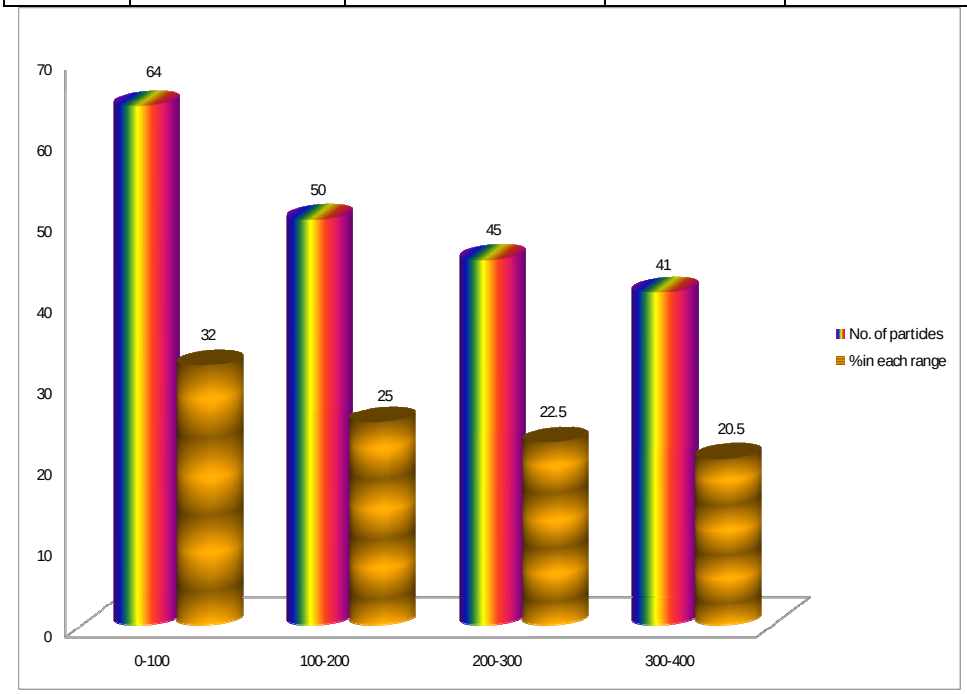
6	RxS06	460	465

6.1.5 PARTICLE SIZE ANALYSIS

For particle size Analysis for formulation RxS01 trial

Table no. 12

S.No.	Size range (micron)	Mean size range (micron)	No. of particles	% in each range
1	0-100	50	64	32
2	100-200	150	50	25
3	200-300	250	45	22.5
4	300-400	350	41	20.5

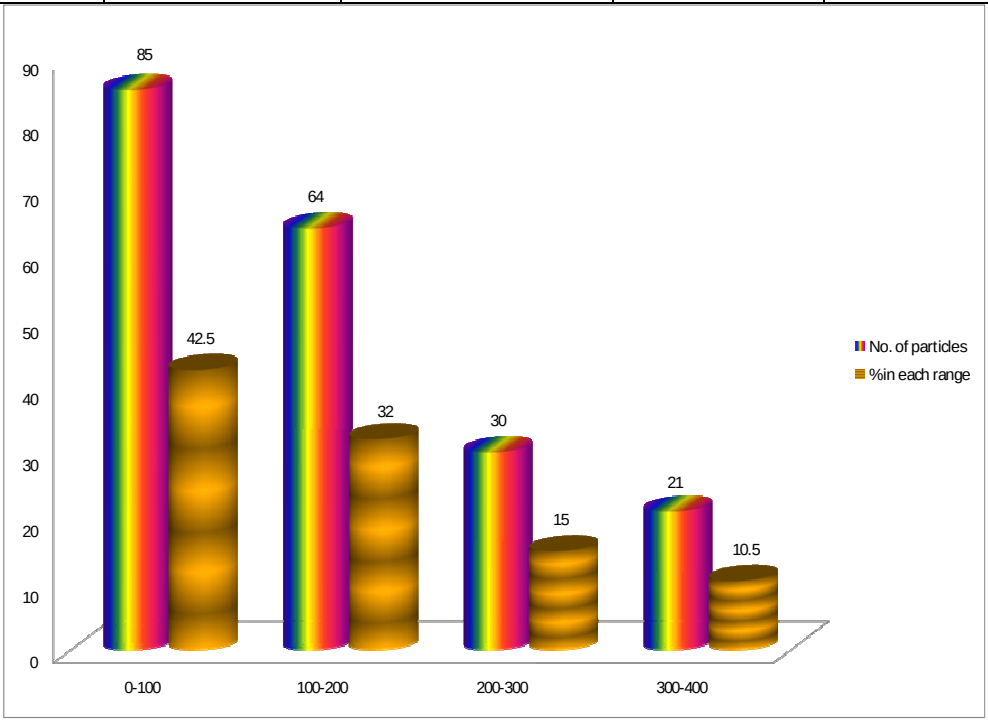


For particle size Analysis for formulation RxS02 trial

Table no. 13

S.No.	Size range	Mean size range	No. of	% in each

	(micron)	(micron)	particles	range
1	0-100	50	85	42.5
2	100-200	150	64	32
3	200-300	250	30	15
4	300-400	350	21	10.5

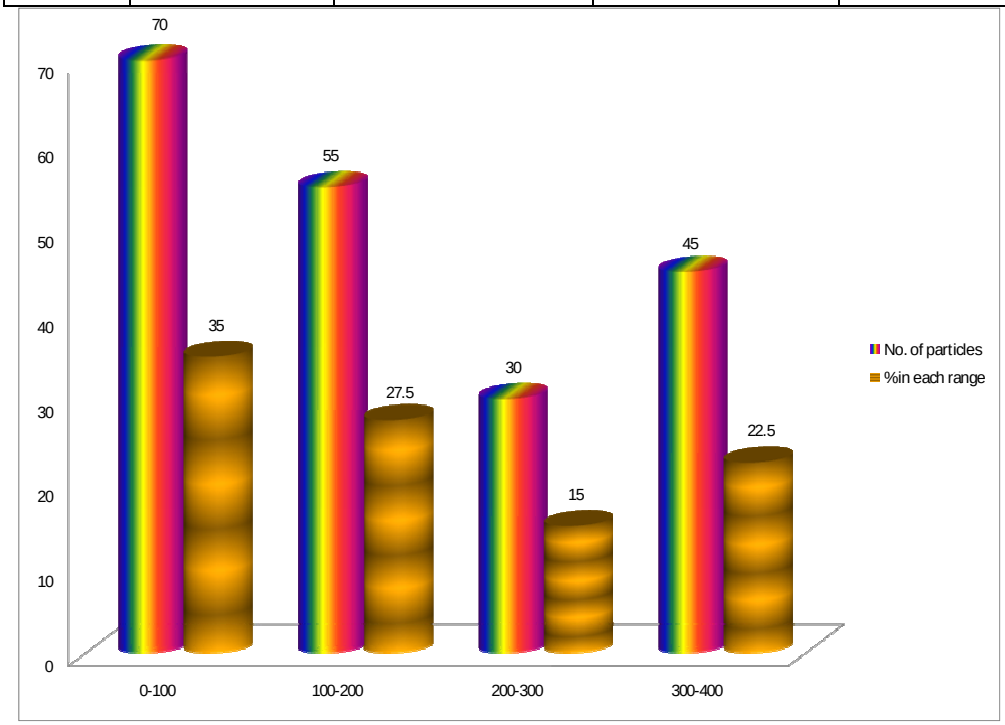


For particle size Analysis for formulation RxS03 trial

Table no. 14

S.No.	Size range (micron)	Mean size range (micron)	No. of particles	% in each range
1	0-100	50	70	35
2	100-200	150	55	27.5
3	200-300	250	30	15

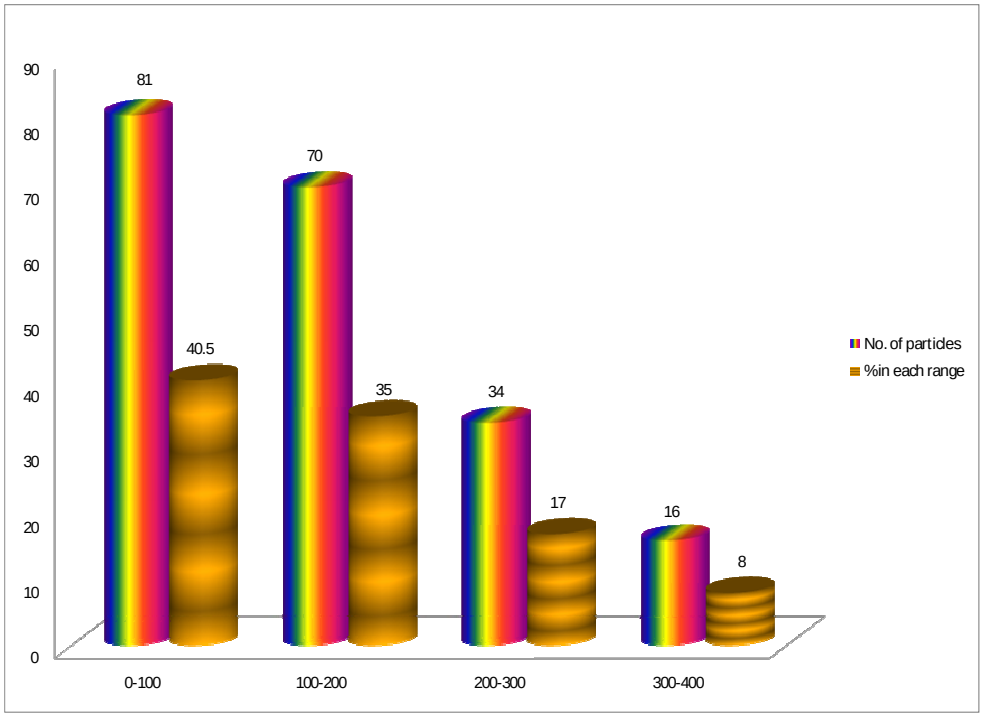
4	300-400	350	45	22.5



For particle size Analysis for formulation RxS04 trial

Table no. 15

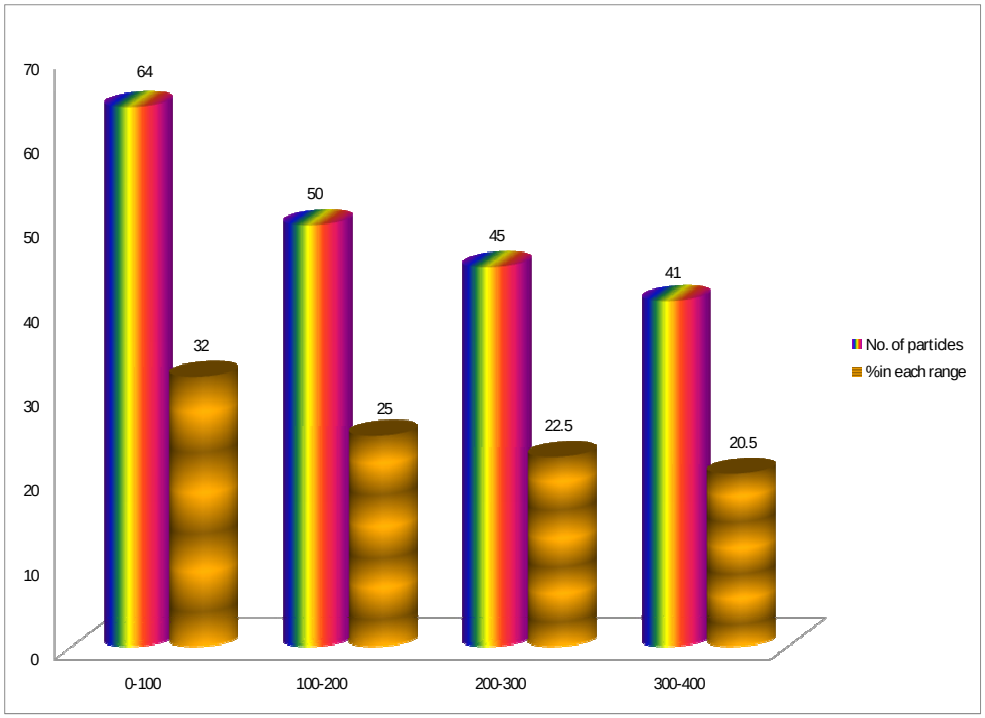
S.No.	Size range (micron)	Mean size range (micron)	No. of particles	% in each range
1	0-100	50	81	40.5
2	100-200	150	70	35
3	200-300	250	34	17
4	300-400	350	16	8



Particle size Analysis for formulation RxS05 trial

Table no. 16

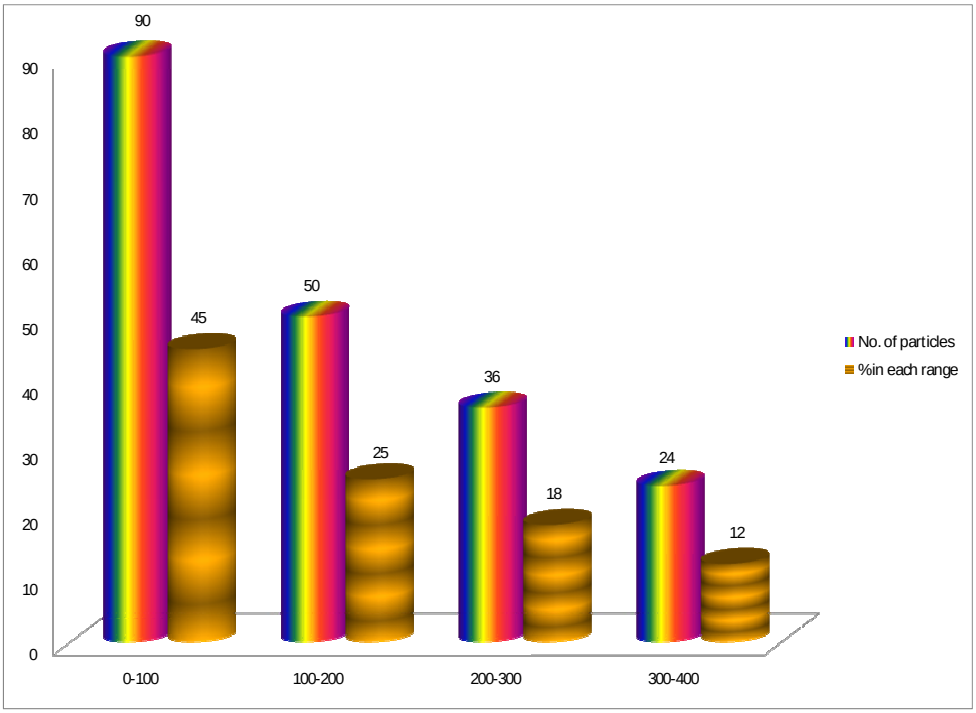
S.No.	Size range (micron)	Mean size range (micron)	No. of particles	% in each range
1	0-100	50	64	32
2	100-200	150	50	25
3	200-300	250	45	22.5
4	300-400	350	41	20.5



Particle size Analysis for formulation RxS06 trial

Table no. 17

S.No.	Size range (micron)	Mean size range (micron)	No. of particles	% in each range
1	0-100	50	90	45
2	100-200	150	50	25
3	200-300	250	36	18
4	300-400	350	24	12



6.1.6 Percentage sedimentation volume

It was checked for all trial formulations after 30 days. The detailed data is given in Table no.8 Among the six formulation

RxS03 and RxS06 gave significantly best percentage sedimentation volume.

Observed percentage sedimentation volume for all trial formulation after 30 days

Table No: 18

S.No.	Formulations	Sedimentation Volume	Average
1	RxS01	96, 99, 98, 96, 98	97.4
2	RxS02	96,98,99,95,97.5	98
3	RxS03	100, 100, 100, 100, 100	100
4	RxS04	99, 99, 99, 99, 98	98.8
5	RxS05	99, 99, 97, 99, 99	98.6
6	RxS06	100, 100, 100, 100, 100	100

6.1.7 Assay:-

The assay of oral suspension is done by UV method. All the six batches observed within the standard range of 90% to 110%. The observed values are given in Table No.19

Assay of Roxithromycin suspension

Table No.19

S.No.	Formulation	Assay %
1	RxS01	92.15
2	RxS02	92.47
3	RxS03	94.015
4	RxS04	93.0
5	RxS05	93.16
6	RxS06	94.47

Calculation: For RxSo6 Trial

$$= \frac{0.4217}{0.4345} x \frac{50.8}{25} x \frac{5}{25} x \frac{100}{12.2} x \frac{50}{25} x \frac{25}{20} x \frac{95.39}{100} x 5 x 1.22$$

$$= \frac{47.23}{50} x 100 = 94.47\%$$

6.1.8 Stability studies conducted after one month and two month in two conditions of 40°C and 31 °C (Room temperature)

6.1.8.1 Stability studies:

Stability study tests are used to find out whether the formulations are maintaining their quality during storage periods or not. Stability tests are used to find out the best formulation the series of formulation. It can be studied by applying a stress to the formulation such as temperature, humidity and light.

Here stability study was conducted for RxSo6 at 40 °C/75% RH

Label Claim:

Each 5 ml contains

Roxithromycin oral suspension 50 mg

Batch No: RxS06

Packing: 50ml Labeled amber coloured bottle

Storage condition: 40 °C ± 2 °C / RH: 75% ± 5%

Table No.20

Test	Specifications	Initial observation	After 1 month	After 2 month
Appearance	Orange coloured, pleasantly flavoured suspension with sweet taste	Confirms	Confirms	Confirms
Weight/ml	1.2 ± 0.2	1.22	1.22	1.22
pH	4 to 5	4.51	4.56	4.55
Assay each 5 ml contains Roxithromycin	90.0% -110%	94.47	94.41	94.35

6.1.9 Microbial Evaluation of the optimized formulation RxS06:-

The microbial; limit test was carried out as per the procedure given section 5.5.10.

The observation of formulation RxS06 complies with the specification.

Since E.coli causes severe dysentery in patients, the absence of the organism in RxS06 claim the formulation was made under controlled conditions.

The result after the incubation time was illustrated in table No.21

The plate counts for TBC and TFC were depicted in figure.

The specific test for E.coli was depicted in Figure no.1

Table No.21

S.No.	Test	Specification	RxS06	Comment

1	TBC	NMT < 100 CFU	< 10 CFU	complies
2	TFC	NMT < 100 CFU	< 10 CFU	complies
3	E.Coli	Negative	Negative	complies

CONCLUSION

The objective of the present study was to develop a stable taste masked roxithromycin oral suspension, which could be palatable for infants and children. Various batches were developed, Among that formulations (Rxso1 to Rxso6) evaluated and discussed. Formulation Rxso6 was found to be having the desirable features of stable suspension such as sedimentation volume, PH, viscosity, assay, microbial limit test. Also when subjected under accelerated condition the suspension behavior was not altered always.

Hence it can be concluded that the bitter taste might be masked through the efficient drug-resin complex,(Roxithromycin-Indion 204)which was the key factor for taste masking.

Further evaluation on taste masking for the formulation Rxs06 shall be studied in future with human volunteer after obtaining ethical committee permission .

From all favorable result it was revealed that formulation Rxs06 can be concluded as the optimized and stable Roxithromycin oral suspension and above evaluation parameter it indicates that the RXS06 are better than the other formulations and also from microbial study it was confirmed that the final formulation(RXS06) also protected from microbial growth hence it is good suspension for administration.