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A STUDY ON SOLUBILITY AND DISSOLUTIONENHANCEMENT OF ERYTHROMY CIN

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ABSTRACT

Aim of the study: Erythromycin is a BCS Class II /IV drug belongingto macrolide antibiotic used in the treatment of a broad variety of infections, of which respiratory tract infections are the primary indication. But Erythromycin has only 50% oral bioavailability, due to its poor aqueous solubility, which limits its potential for optimal drug delivery and therapeutic effect. Its poor solubility is thus an obstacle in formulation development. So it is more cost effective to chemically re-design a molecule than to move through the whole development process, it is crucial to develop a formulation that overcomes problems of insolubility. The aim of this study to enhance the solubility of Erythromycin by using its solvates. **Objective of the study:** The objectives of this study to enhance thesolubility and Dissolution by To Prepare Erythromycin solvates using Choloroform and Ethanol as solvents To characterise the different forms prepared; To evaluate the Solvated form forms on their solubility and Dissolution To find the suitability of Solvated form in Pharmaceutical Formulation. **Plan of work:** The present work carried out to solubility and dissolution enhancement of Erythromycin which is having low bioavailability due to its poor aqueous solubility. So study was carried out to enhance the Solubility and dissolution of Erythromycin in the following steps Literature survey, Procurement of drug and Chemicals, Preformulation of Erythromycin, Preparation of Erythromycin Solvates Characterisation of Erythromycin Solvates Formulation of Erythromycin Solvates **Conclusion:** According to recent estimates, nearly 40% of new chemical entities are rejected because of poor solubility i.e. biopharmaceutical properties. Poor Solubility of drug may result in inadequate bioavailability and thus in ineffective treatment regimes. Similarly, Erythromycin also has a poor solubility profile and the form available on the market is mostly the stable, crystalline monohydrate with the oral bioavailability 50%. So the Objective of the present study to enhance the solubility and dissolution of Erythromycin using solvates. Two solvate forms of Erythromycin were prepared by recrystallisation using chloroform and ethanol solvents. It was found that the Solvates showed better solubility and dissolution profile compared to Erythromycin. Among Solvate Choloroform solvate showed better solubility and Dissolution profile than Ethanol solvate. The tablets of Choloroform solvates were formulated by direct compression method to find the suitability of Solvates in the formulation of Pharmaceutical Dosage form by comparing Freshly Prepared Choloroform Solvates against 3 months old choloroform solvate. The variants of solvates were used to find out the stability of solvates. Based on the evaluation of tablets it was found that During storage the solvates transformed in to more crystalline substance which may affect dissolution profile from the dosage. From the study it was concluded that solvates can be used to enhance the solubility and dissolution of Poorly soluble drugs.

INTRODUCTION

Modern pharmaceutical technology is concentrated on new drug forms which are targeted to the exact site at the appropriate time, with maximum efficiency and with reduced side-effects. Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules. 3According to recent estimates, nearly 40% of new chemical entities are rejected because of poor solubility i.e. biopharmaceutical properties.[1]

The solubility properties of drugs and the dissolution of

the active substance from dosage forms have a basic impact on the bioavailability of the product. Enhancement of the solubility of poorly-soluble drug substances is one of the most important tasks in pharmaceutical formulation development.[2] The drug substances are categorized into four classes based on their solubility parameter and permeability to bio-membranes, and such a classification system is called as a Biopharmaceutical Classification System (BCS). The BCS guidance takes into account three major factors, dissolution, solubility, and intestinal permeability, which govern the rate and extent of drug absorption from immediate release solid dosage forms. The concept of BCS provides a better understanding of the relationship betweendrug release from the product and the absorption process.[3]

List of materials

Table No. 01: List of materials.

S. NO.	Materials	Manufacturer
01.	Erythromycin	GIFT sample from Sun Pharmaceuticals
02.	Ethanol	Sisco research laboratory
03.	Chloroform	Sisco research laboratory
04.	Microcrystalline Cellulose	GIFT sample from Microlabs
05.	Talc	Sd fine Chemicals,Mumbai
06.	Sodium Starch Glycolate	Sd fine Chemicals,Mumbai
07.	Magnesium Sterate	GIFT sample from Microlabs

Experimental investigations

Preformulation studies

Preformulation testing is an investigation of physical and chemical properties of drug substances alone and when combined with excipients. It is the first step in the rational development of dosage forms. The overall objective of preformulation testing is to generate information useful to the formulation in developing stable and bioavailable dosage forms. The use of preformulation parameters maximizes the change in formulating an acceptable, safe, efficacious and stable product.

Identification of drug

The identification of drug was done by FTIR spectroscopy. Erythromycin mixed with suitable quantity of potassium bromide. About 100mg of this mixture was compressed to form a transparent pellet using a hydrallic press at 10 tons pressure. It was scanned from 4000 to 500cm^{-1} in a FTIR Spectrophotometer. The FTIR spectrum of pure drug Erythromycin is shown in Figure.

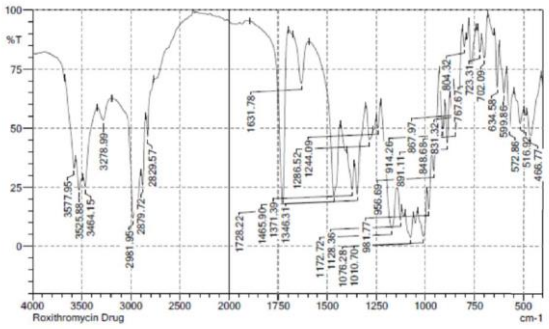

Figure No. 01: Identification of drug.

Preparation of erythromycin solvates

The solvate of Erythromycin was prepared by recrystallization of the raw material from Solvent (Chloroform, Ethanol). Approximately 5 g of Erythromycin was added to 50 mL of Solvent while stirring continuously and heating the solution to approximately 60°C in a magnetic stirrer for 4 hours. After slow evaporation of the Solvent, a dense mass was obtained. This mass was dry but tend to stick to the surfaces of containers. The desolvated solid was prepared by placing the Erythromycin solvate in a Dessicator at room temperature for 48 hrs. Then it was triturated and stored in airtight container.

Table No. 02: Formulation code for erythromycin solvate.

Material	Formulation code
Erythromycin	F 1
Erythromycin Choloroform Solvate	F2
Erythromycin Ethanol Solvate	F 3

Characterization of erythromycin solvates

The prepared Erythromycin solvates were cha acterized by the following reanalytical methods were used to differentiate their crystalline nature and its role in solubility.

Ftir studies

The structural changes due to drug solvent interaction drug was done by FTIR spectroscopy. Erythromycin and Solvates were scanned from 4000 to 500cm-1 in a FTIR Spectrophotometer. FTIR spectra of F1,F2,F3 were given below.

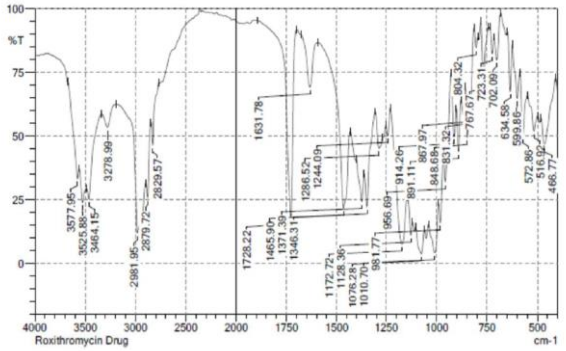

Figure no. 02: FTIR Studies of Erythromycin.

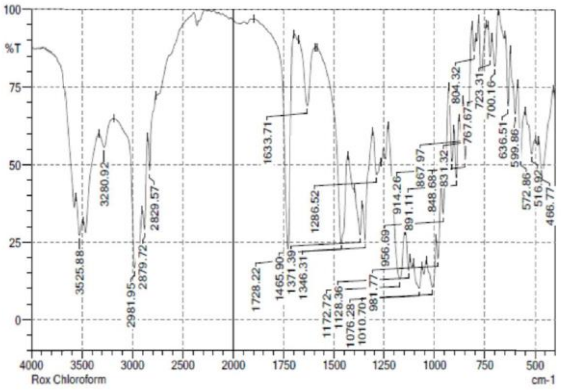

Figure No. 03: FTIR Studies of Erythromycin chloroform Solvate.

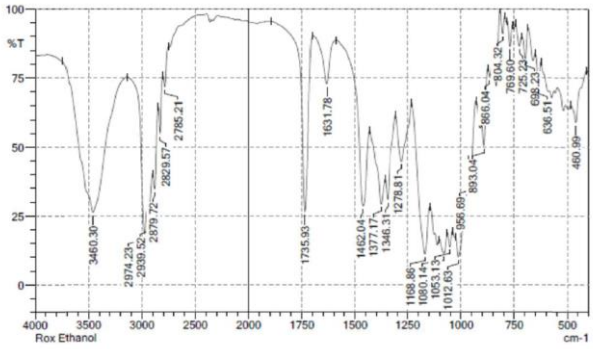

Figure No. 04: FTIR Studies of Erythromycin Ethanol Solvate.

Formulation of tablets

The Erythromycin Tablets were prepared by Direct Compression method perthegiven formula in Table.

Formulation

Stage-1: The Erythromycin Powder was sifted through 40 # mesh.

Stage-2: All the materials required as per the formulae were blended in aclosedpolyethylene bag and mixed well.

Stage-3: The blends were sifted through 20# mesh.

Stage-4: The lubrication materials Starch talc, and magnesium stearate were sifted through 40# mesh and added into the sifted granules and lubricated.

Stage -5: The blend is compressed into tablets by using Rotary tablet compression machine After the compression of tablets were tested for physical parameters.

Table no. 03: Formulation of tablet.

Ingredients	F4	F5	F6
Erythromycin	75 mg	75 mg	75 mg
Micro crystalline Cellulose	110 mg	110 mg	110 mg
Sodium Starch Glycolate	15 mg	15 mg	15 mg
Talc	4 mg	4mg	4 mg
Magnesium Sterate	1 mg	1 mg	1 mg

F4-Pure Drug
F5- Choloroform Solvate (Fresh Solvate)
F6 –CholoroformSolvate (3 months Old)

Evaluation of fabricated tablets
Physical characteristics of formulated tablets were evaluated for tablet size,hardness, friability, and weight variation.

Hardness
The hardness of the tablet was tested by using Pfizer hardness tester. Theresultswas shown in Table No-

Friability
It was done in Electro lab friabilator apparatus where the tablets were subjected to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25rpm dropping the tablets at a distance of six inches with each revolution. Preweighed samples of 20 tablets were placed in the friabilator, which is then operated for 100 revolutions. The tablets are then dusted and reweighed. Conventional compressed tablets thatlose less than 0.5 to 1.0 of their weight as generally considered acceptable. The results wereshown in Table No-12.

$$\text{Friability} = \frac{W1 - W2}{W1} \times 100$$

Weight variation test
Twenty tablets were randomly selected form each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated. Thebatch passes the test for weight variation test if not more then two of the individual tablet weight deviate from the average weight by more than the percentage shown in Table, and none deviate by more than twice the percentage shown. The results were shown in Table.

Table No. 04: Weight variation tolerance for tablet (USP).

Percentage deviation allowed under weight variation test.	
Average weight of tablet (X mg)	Percentage deviation
X < 130 mg	10
130 < X < 324 mg	7.5
X > 324 mg	5

Percentage deviation allowed under weight variation test. The observations of weight variation test of each batch are shown in Table No: 05

Disintegration test
The tablets were taken in a rigid basket rack assembly supporting six cylindrical glass tubes. The assembly was suspended in the liquid medium in a 1000 ml beaker. The volume of liquid was such that, wire mesh at its lower point was at 25 mm below the surface of the liquid and its lower point was at 25 mm above the bottom of the beaker. A temperature was maintain at 37 ± 2^0C. Finally the average disintegration time was recorded.

The value of the disintegration time of all the batches given in the Table No-05.

Drug content uniformity
5 tablets were powdered and powder equivalent to 75mg of drug was weighed and taken in a 50ml volumetric flask volume was made with Phosphate Buffer pH 6.0. The filtered using 0.2 µ membrane filter. From filtrate, 10 ml of solution was pipette out and diluted up to 100 ml with the phosphate buffer pH 6.0, and absorbance was measured at 205 nm using UV double beam spectrophotometer.

The value of the disintegration time of all the batches given in the Table No-05.

Table No. 05: Evaluation of fabricated tablets.

Mulation code	Tegration Time (in minutes)	Hardness Kg/Cm^2	Weight Variation	Riability (%w/w)	% Drug Content
F4	4.00	4.5	199	0.12	97.25
F5	4.23	4.2	203	0.16	98.13
F6	4.12	4.0	200	0.13	96.54

In-vitro drug release

In-vitro drug release study was performed using type 1 of IP (paddle) at a speed of 100 rpm. The medium was Phosphate buffer 6 (900 ml) maintained at 37°C±0.5°C. The dissolution test was conducted for 45 minutes; samples of 5 ml werewithdrawn in the interval of 10,20,30,45 minutes with replacement of equal volume of dissolution medium. The withdrawn samples were filtered and the concentration of Erythromycin was measured by determining absorbance at 205 nm using UV spectrophotometer.

Table No. 06: In-vitro drug release.

S. No	Time in minutes	% Drug Release		
		F4	F5	F6
1	10 min	25.49	31.57	24.28
2	20 min	39.83	47.49	35.61
3	30 min	50.52	61.25	49.85
4	45 min	62.75	76.58	64.31
5	60 min	72.08	88.14	71.25

RESULTS AND DISCUSSION

Erythromycin has only 50% oral bioavailability, due to its poor aqueous solubility, which limits its potential for optimal drug delivery and therapeutic effect.The aim of this study to enhance the solubility of Erythromycin by using its solvates.

Identification of drug

The drug were identified using FTIR Spectra.

Phsyical characterisation

Solubility studies

From the solubility studies it was found that Erythromycin have better Solubility in Phosphate Buffer pH 6 compared to other solvents. Solubility of Erythromycin is on the below order.

Water < 0.1 N Hcl < Phosphate Buffer pH 6

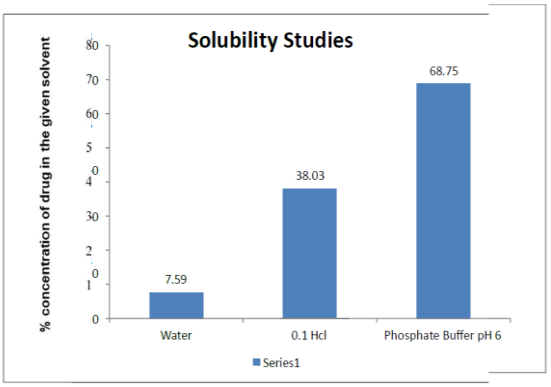

Figure no. 05: Solubility studies of erythromycin.

Preformulation studies of erythromycin

Bulk density, tap density, obtained bulk density and tap density values, loss on drying, compressibility index was calculated. The drugare poor flow and low compressibility. Good flow of powder /granules is essential in tableting because the flow property and compressibility is likely to influence the compression process in the preparation of tablets.

The moisture content has influence on solubility & Formulation process in various aspects like sticking and also affects the moisture sensitivity drugs. The LOD for Erythromycin was 2.2 %.

Preparation of erythromycin solvates

Erythromycin is poorly water soluble and an improvement in its solubility could result in an improvement in its bioavailability. So solvates of Erythromycin was prepared by recrystallization by using Chloroform (F2), Ethanol (F3) as solvents.

Characterization of erythromycin solvates

Ftir studies

Overlapping of F1, F2, F3 FTIR Spectra didn't show much variation in the FTIR spectra of solvated Erythromycin (F2, F3) compared to Roxitromycin (F1). So It revealed that that solvates didn't cause much variation in Chemical Structure of Pure Drug.

Ftir spectra of F1,F2,F3

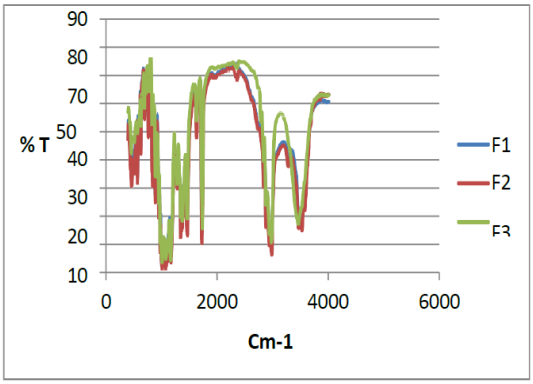

Figure no. 06: Comparative FTIR Spectra.

SEM Analysis: [Scanning electron microscope]

SEM microscopy images of the solvates were compared with that of the Erythromycin, It was found that the Erythromycin(F1) has a striated appearance with more crystalline structure compared to Chloroform solvate (F 2) which has a smooth surface and Ethanol solvate (F 3) which has a partial smooth surface which was shown in given Figure.

SEM of Erythromycin	F Chloroform Solvate	SEM of Ethanol Solvate

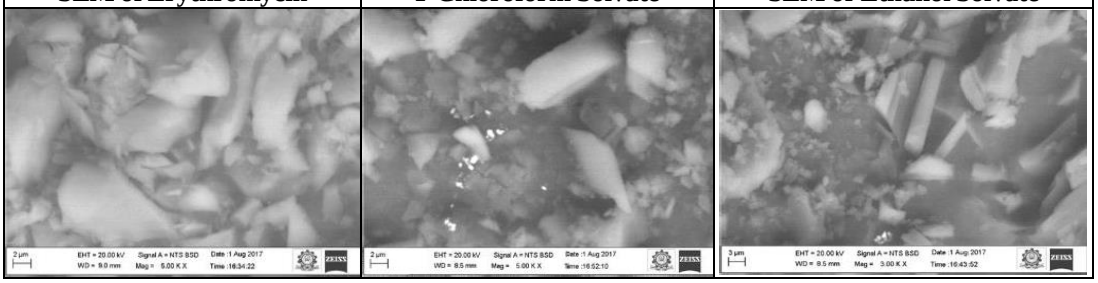

Figure no. 07: Comparat ve SEM.

Aqueous solubility studies

Aqueous solubility studies indicated that solvates has increased the solubility of Erythromycin. The chloroform solvates show d better aqueous solubility Compared to pure drug and ethanol solvate. The aqueous solubility was in the following order.

F1 < F3 < F2

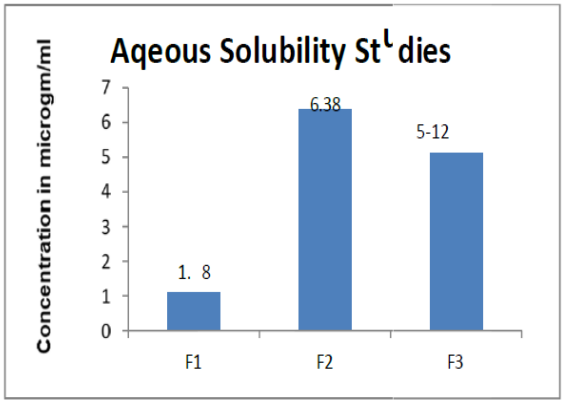

Figure no. 08: Aqueous solubility studies of solvates.

Dissolution studies

The Chloroform solvate(F2) showed better in vitro release profile compared to Pure Drug (F1) and Ethanol Solvate (F3). The Pure Drug showed a release of 38% release in 60 minutes. But solvates showed enhanced dissolution properties compared to pure drug may be due to reduction in crystalline nature of drug during salvation. The invitro release was in the following order.

F1 < F3 < F2

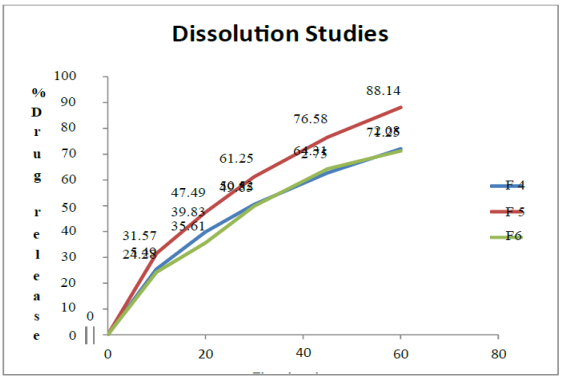

Figure no. 09. Invitro release profile of solvates.

Formulation and Evaluation of tablets

Three differen Erythromycin (F4) batches of Erythromycin Tablets were formulated using Pure reshly Prepared Erythromycin Chloroform Solvate (F5) and 3 months old Erythromycin Chloroform Solvate (F6) to find the possib lities of usage of solvates in the formulation of Dosage form and to know the ability of solvates to retain its reduced crystallinity property. Tablets were prepared by direct compression method using micro crystalline cellulose as direct compression filler and Sodium Starch Glycolate as disintegrant. The formulated tabletsthe following parameters were ta**b**ulated in the given tables.

Table no. 07: Evaluation of fabricated tablets.

Formulation code	Disintegration Time (in minutes)	HardnessKg/ Cm^2	Weight Variation	Friability (%w/w)	% Drug Content	Limit
F4	4.00	4.5	199	0.12	97.25	Complies
F5	4.23	4.2	203	0.16	98.13	Complies
F6	4.12	4.0	200	0.13	96.54	Complies

CONCLUSION

According to recent estimates, nearly 40% of new chemical entities are rejected because of poor solubility i.e. biopharmaceutical properties. Poor Solubility of drug may result in inadequate bioavailability and thus in ineffective treatment regimes. Similarly, Erythromycin also has a poor solubility profile and the form available on the market is mostly the stable, crystalline monohydrate with the oral bioavailability 50%.So the Objective of the present study to enhance the solubilityand dissolution of Erythromycin using solvates. Two solvate forms of Erythromycinwere prepared by recrystallisation using chloroform and ethanol solvents. It was found that the Solvates showed better solubility and dissolution profile compared to Erythromycin. Among Solvate Choloroform solvate showed better solubility and Dissolution profile than Ethanol solvate.

The tablets of Choloroform solvates were formulated by direct compression method to find the suitability of Solvates in the formulation of Pharmaceutical Dosage form by comparing Freshly Prepared Choloroform Solvates against 3 months old choloroform solvate.

The variants of solvates were used to find out the stability of solvates. Based on the evaluation of tablets it was found that During storage thesolvates transformed in to more crystalline substance which may affect dissolution profile from the dosage.

From the study it was concluded that Solvates can be used to enhance the solubility and dissolution of Poorly soluble drugs

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