FORMULATION AND EVALUATION OF A SOLID DISPERSION TECHNIQUE AND ROXITHROMYCIN USING HYDROPHILIC CARRIERS LOADED IN TO MICROSPHERES FOR THE TREATMENT OF PERIODONTITIS

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Abstract:

In the current investigation, we sought to produce roxithromycin by the use of a solid dispersion approach that used hydrophilic carriers loaded into microspheres. In order to make the solid dispersions, urea and mannitol were combined together and melted into position as hydrophilic carriers. Studies that were conducted using DSC and SEM provided evidence that a complex developed between them despite the absence of any interaction. On the other hand, the initial dissolving rate of roxithromycin was improved with the assistance of solid dispersion's that were based on HPMC and PEG6000. In this case, the formulation RXM HP3, which is a solid dispersion created between roxithromycin and HPMC, was found to have the greatest dissolving rate; nevertheless, RXM PG3 was reported to have the best stability. Based on the findings regarding its solubility and stability, RXM HP3 was chosen as the formulation with the best overall performance.

Keywords: Controlled release,Fusion method,Roxithromycin,Microspheres,Solid dispersions
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INTRODUCTION:

Positive outcomes related with oral drug administration include excellent patient compliance, accurate dose, cheap cost, and prolonged stability[1]. Several methods have been disclosed for describing controlled drug delivery systems that allow for prolonged drug release into the gastrointestinal tract with the necessary release characteristics[2]. The fundamental challenge in developing oral controlled delivery systems for drugs that are insoluble in water is, however, drug disintegration[3]. Therefore, to maximise therapeutic benefits, a more secure and efficient delivery mechanism is necessary. The Noyes-Whitney equation suggests that smaller particles are preferable for facilitating dissolution. Multiparticulate systems are considered to be among the most efficient means of medication delivery[4]. There has been a lot of interest in microspheres, a kind of microparticulate medication delivery technique, during the last two decades. But altering the particle size alone is not enough to increase the bioavailability of certain weakly water-soluble medications[5]. This highlights the significance of considering the potential for additional physical changes, such as the control of drug release from their formulations[6].

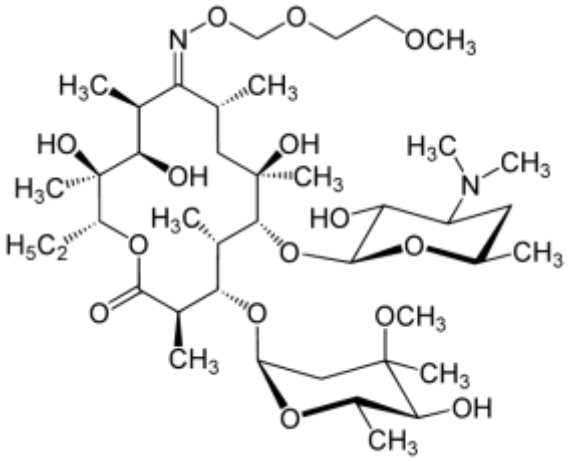


Fig. 1: Structure of Roxithromycin

Solid dispersion technology is among the most efficient means of enhancing the relative bioavailability of drugs that aren't particularly water-soluble. Hydrophilic carriers such mannitol, hydroxypropyl methylcellulose, polyethylene glycols, polyvinylpyrrolidone, and urea have been examined in connection to the dissolving behaviour and bioavailability of poorly water-soluble medications[7].

This semisynthetic macrolide antibiotic is called roxithromycin. This medicine may be used to treat infections of the respiratory tract, urinary tract, and soft tissues. Roxithromycin, like erythromycin, has a lactone ring with 14 members. In this case, the lactone ring has an N-oxime connected as a side chain. Moreover, it is now being studied in clinical trials for its potential use in treating male-pattern baldness[8].

The invention was patented in 1980, and by 1987 it had undergone sufficient testing to be used in medical settings. It's important to remember that you may get roxithromycin under a variety of brand names. Unfortunately, you cannot purchase roxithromycin in the United States. Roxithromycin may be purchased in New Zealand, Australia, Canada, France, Germany, Israel, South Korea, and South Korea. The effectiveness of roxithromycin as an antimalarial has also been investigated[9].

The most often reported unwanted effects were diarrhoea, nausea, vomiting, and stomach pain. Skin rashes, abnormal liver function levels, and altered olfactory or gustatory perception are some of the rarer side effects that may occur anywhere in the neurological system.By having a lower affinity for cytochrome P450 than erythromycin, roxithromycin is less prone to cause medication interactions.There are no known drug interactions between roxithromycin and

hormonal contraceptives, prednisolone, carbamazepine, ranitidine, or antacids[10].

When roxithromycin is administered with theophylline, plasma concentrations of theophylline may increase, according to certain studies. The plasma levels of patients who start treatment with a high theophylline dosage should be monitored, although dose adjustments are usually not required[11].

The antibacterial drug roxithromycin seems to interact with the blood thinner warfarin. There is a correlation between the use of roxithromycin and warfarin, and an increase in prothrombin time and/or international normalised ratio in the patient (INR). The result has been prolonged spells of severe bleeding[12].

Antibacterial roxithromycin works by preventing bacteria from producing proteins they need to survive and multiply. Binding of roxithromycin to the 50S subunit of the bacterial ribosome blocks the production of peptides. Despite the fact that both erythromycin and roxithromycin are effective against germs, roxithromycin is more effective against specific gram-negative bacteria, such as Legionella pneumophila.Solid dispersions and microspheres were made using both fusion and solvent evaporation methods in this study[13].

In this case, the solid dispersion containing RXM drug was prepared using the co-precipitation method, in which HPMC polymer and PEG 6000 polymer were weight accurately in the different ratios, and then dissolved with the drug in the mixture of methanol: dichloromethane (1:2) for HPMC polymer, and methanol alone for PEG 6000 polymer, to get proper dispersion with drug. Fill the heated test tubes with the drug polymer solution. After the solvent has been evaporated at 700 degrees Celsius in a vacuum, the complex form is dried in a dessicator. After being dried in desiccators for 24 hours, the complex is weighed and measured to assure consistency in its components. The crystalline mass was ground into a powder and passed through a No. 120 mesh screen[14].

METHODOLOGY

Preparation of Complex

Preparation of sold dispersion

Here the solid dispersion containing RXM drug were prepared with the help of co-precipitation method, in which both the polymers were weight accurately in the different ratios and then dissolve with the drug in the mixture of methanol: dichloromethane (1:2) for HPMC polymer and methanol alone for PEG 6000 polymer to get proper dispersion with drug. Transfer the drug polymer solution to the test tubes that are maintained at high temperature. The solvent then evaporated under vacuum at 70^{o} and dried in a dessicator until complex form gets dried. In the end dried form of complex kept in desiccators for 24 hrs to attain constant weights. The solidifies mass were crushed, pulverized and passed through mesh No. 120[15].

Table 1: List of Carriers and their ratio with RXM

Formulation Code	Carrier	Ratio Drug: Carrier	Method
SD PEG 0.5 SD PEG 1 SD PEG 3	PEG 6000	1:0.5 1:1 1:3	Co- Precipitation method
SD HPMC 0.5 SD HPMC 1 SD HPMC 3	HPMC	1:0.5 1:1 1:3	Co- Precipitation method

Characterization of complexes

Differential Scanning calorimetry

Liquid nitrogen gas was employed as a coolant for DSC (DSC Q20 V24.4 Build 116, USIC, K.U. Dharward, India) experiments, and the samples were placed, measured, and weighed in sealed aluminium pans. The sample was then heated or cooled at a constant rate of 100 degrees Celsius per minute throughout a temperature range of 40 to 300 degrees Celsius. DSC thermograms of pure RXM, HPMC and PEG with their exact ratio of complex byCSE method were determined[16].

Scanning Electron Calorimetry

SEM images related with shape and surface morphology of solid formulation, which were recorded for studying by using scanning electron microscopy, with the help of metal stubs, which is used for mounting microspheres and double sided adhesive tape were used on metal stubs and this metal stubs is coated with the help of gold film including sputter coater for the attachment with the SEM instrument using JSM 6400 SEM, which help to provide up to 50X magnification of the powder drug or formulation and give the image with SEI (secondary electron image) which is a detector of surface of the formulation and 0.6mm hg pressure were maintained at throughout process (Jeol Ltd., Akishima,Tokyo)[17].

Evaluation Parameter of Complex

Determination of percent yield

We begin by weighing 50 mg of RXM containing solid dispersion; next, we crush the solid dispersion using a pestle and mortar; finally, we dry the mixture for 4-5 hours in desiccators and pass it through a sieve with a mesh size of 80; finally, we re-weigh the material, entering the necessary values into the formula below; finally, we calculate the percent yield from this data[18].

Percent yield = Solid dispersion actual weight/ Roxithromycin weight + other excipients use in preparation) × 100

Determination of Drug content

Roxithromycin content in physical mixtures and solid dispersions analyzed properly by Accurately weight samples (10 mg) of the mixture were dissolve in 0.8 ml of methanol and volume was made up to 10ml with double distilled water. This solution further suitably diluted with double distilled water and the absorbance was measured at 204 nm using UV/Visible spectrophotometer[19].

***In-vitro* dissolution rate study**

Using the USP XXI six stage dissolution rate test apparatus with the paddle method, the in-vitro dissolution profile of pure Roxithromycin, formulations of physical mixtures, and solid dispersions of Roxithromycin were studied at 37 0.50 degrees Celsius, with the dissolution medium consisting of 900 ml of double-distilled water maintained at 50 revolutions per minute. At 5, 10, 20, 30, 40, 50, and 60 minutes, five-milliliter samples were taken and analysed for Roxithromycin concentrations using a UV/Vis spectrophotometer at 207 nm; a graph showing the cumulative percent drug release vs time was also constructed 20.

Stability Studies

Selected formulation was stored in a vials covered with screw cap and stored them in stability chamber at 40^{o} C± 2^{o} C and maintain 75% relative humidity (RH) ±5% for given time period (3 months). Then samples were drawn at different time interval on a regular basis and analyzed for physical appearance, drug release or dissolution studies and drug content and other type of studies which is finally result on the basis of how much drug is left in formulation, which is analyzed through UV spectroscopy.

RESULTS AND DISCUSSION:

Determination of Melting point

Melting point of roxithromycin (RXM) measured as 121°C-122°C which is close enough to literature value and also indicating that the sample is pure and identify in a well manner.(B.P., 2004).

UV Spectrophotometry

The maximum absorbance (λ_{max}) of RXM in various physiological pH media, such as phosphate buffer (pH 6.8) and distilled water, was determined using spectrophotometric analysis. All the values were complied with the literature value as given in Table 3.1.

Table 2: Spectrophotometric determination of RXM

S.No.	Media	Litreture value (λ_{max})	Experimental value (λ_{max})
1.	Phosphate buffer, pH 6.8	……nm(B.P. 2004)	204 nm
2.	Distilled water	-	212 nm

Preparation of calibration curve

Calibration curve of RXM in Phosphate buffer, pH 6.8

The RXM calibration curve was made in a 6.8-pH phosphate buffer. Figure 2 displays a scatter plot of absorbance against concentration.

Table 3: Calibration curve data of RXM in Phosphate buffer, pH 6.8

Serial number	Calculated Concentration(µg/ml)	Roxithromycin Absorbance
1	1	0.024± 0.0
2	2	0.096± 0.0
3	3	0.174± 0.0
4	4	0.245± 0.0
5	5	0.326± 0.0
6	6	0.407± 0.0

*All values are expressed as mean ± S.D.

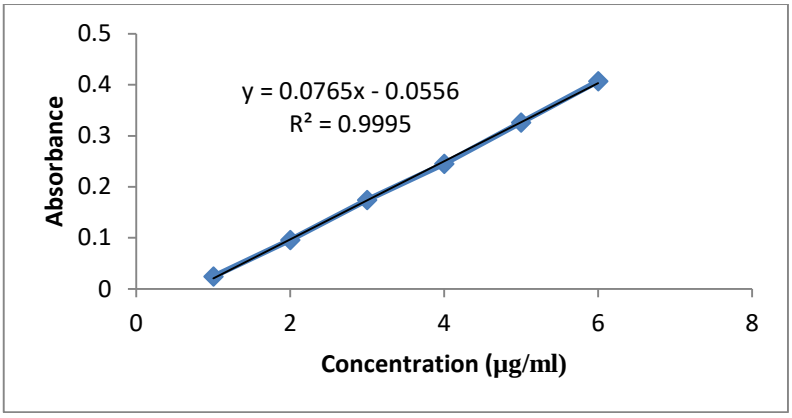


Fig. 2: Calibration curve of Roxithromycin in phosphate buffer (pH 6.8)

Calibration curve of RXM in Distilled water

The standard calibration curve was obtained by preparing stock solutions in distilled water with concentrations ranging from 1 to 6 g/ml. Fig 3 displays the absorbance *vs*. concentration plot.

Table 4: Calibration curve of RXM in Distilled water

S. no.	Calculated concentration(µg/ml)	Roxithromycin (Abs)
1	1	0.044 ± 0.00
2	2	0.175 ± 0.00
3	3	0.325 ± 0.00
4	4	0.471 ± 0.00
5	5	0.633 ± 0.00
6	6	0.781 ± 0.00

*All values are expressed as mean ± S.D.

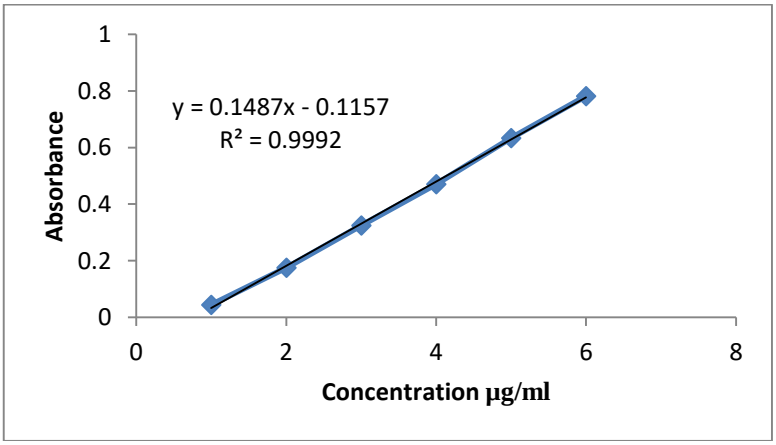


Fig. 3: Calibration curve of RXM in Distilled water

Validation with Analysis **Linearity**

Calibration curve of RXM calculated under given range of 1-6 µg/ml. Using the linear least squares regression, in the calibration curve of RXM (µg/ml) in phosphate buffer, pH 6.8 and linear equation reported as Y = 0.076 x - 0.055 with r^2= 0.9996 having limit of detection (LOD) and limit of quantification (LOQ) 0.041µg/ml and 0.124 µg/ml, respectively. While for calibration of RXM in double distilled water, the linear line equation was y= 0.148x – 0.115 with r^2= 0.9997, with LOD and LOQ value 0.107µg/ml and 0.324µg/ml finally.

Precision with accuracy

The pH 6.8 phosphate buffer calibration curve had intra- and inter-day precision values ranging from 0.150 to 0.751 percent. For double distilled water, it was ranged from 0.114 to 1.025%.

Recovery

Mean percent recoveries in different media are given in the (Table 5). Percent recoveries of RXM for the calibration curve in phosphate buffer, pH 6.8 and distilled water were 98.566 -104.76%, 99.1- 102.1 and 97.5 – 109.2 %, respectively.

Table 5: Validation of analytical method of phosphate buffer pH 6.8 and double distilled water

Parameters	Phosphate buffer, pH 6.8	Double Distilled Water
Accuracy (% Recovery)	98.566-104.76 %	97.5-109.2 %
Regression line equation	Y=0.076x+0.055	Y=0.148x+0.115
(r^2)	0.9996	0.9997
Precision value of Intraday (%RSD)	>2	>2
Presicion value of Interday (%RSD)	>2	>2
LOD (µg/ml)	0.041	0.107
LOQ(µg/ml)	0.124	0.324

Equilibrium solubility

The solubility of roxithromycin in distilled water was found to be 4.86µg/ml. In presence of PEG at ratio of 1:0.5, 1:1 and 1:3 solubility enhancements was found to be 15.771, 57.718, 76.176 respectively. Whereas in presence of HPMC at ratio of 1:0.5, 1:1, 1:3%, solubility enhancement was found to be 29.051, 67.162, 78.997 %. So, this is clear that by using HPMC and PEG, improved the solubility of roxithromycin by forming soluble complexes and solubility of Roxithromycin was found to be directly proportional to the increment in the concentration of polymers like HPMC and PEG. The solubility of Roxithromycin was found higher in percent in presence of HPMC then in PEG this is because of the reason that drug is more soluble with the HPMC because of the more wetting of the drug. The solubility of Roxithromycin in various concentrations of polymers was determined by phase solubility studies. This might be attributable to an improvement of wetting of drug particles and localized solubilisation by the hydrophilic polymers. Among the various hydrophilic polymers, solid dispersion using HPMC with drug at the ratio of 3:1 shows highest saturation solubility than solid dispersion. From the result of phase solubility analysis it can be clearly established that the carriers like HPMC and PEG are having very good solubility enhancing property.

Table 6: Solubility data of roxithromycin in distilled water in the presence of excipients

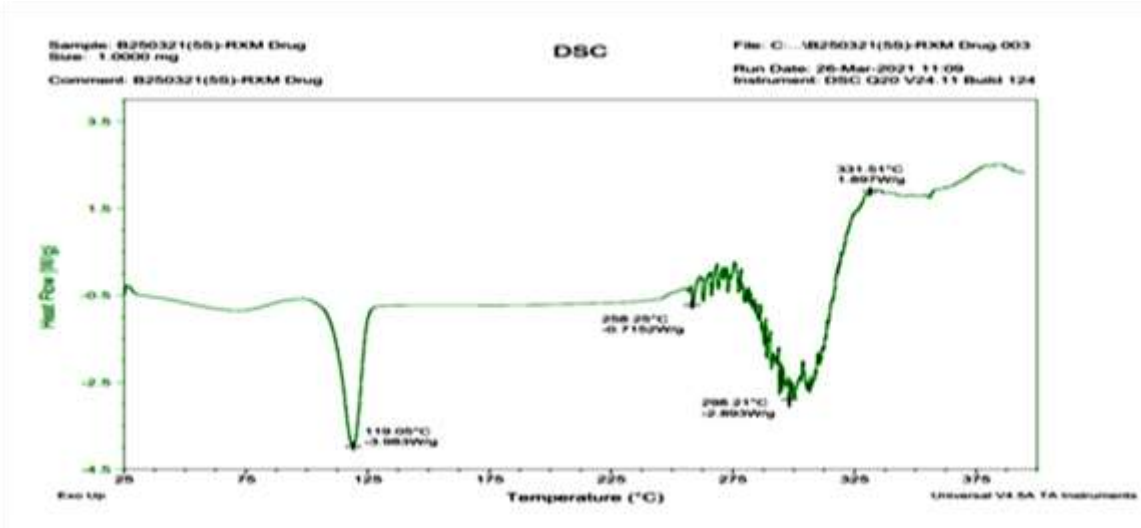
Sample composition	Ratio of carriers	Solubility (µg/ml)	% Solubility enhancement
Drug	------	4.86	------
Drug+ PEG	1:0.5	5.77	15.771
Drug+ PEG	1:1	11.35	57.718
Drug+PEG	1:3	20.40	76.176
Drug+ HPMC	1:0.5	6.85	29.051
Drug+HPMC	1:1	14.80	67.162
Drug+ HPMC	1:3	23.14	78.997

PEG = PEG 6000, Drug= Roxithromycin

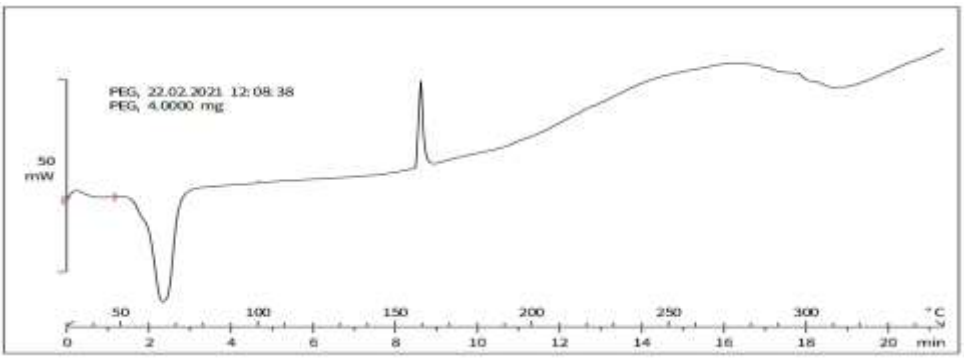
Characterization of complex

DSC

Both the Complex (roxithromycin with PEG 6000 and roxithromycin with HPMC) formed with the help of co-precipitation method was analyzed through DSC thermal curves. In a given thermal curves of roxithromycin, PEG 6000 and HPMC in figure 4a, 4b and 4c, all observed with the endothermic peak at 298ºC, 60ºC, 280ºC proved that they start melting at their respective melting point, whereas in case of complex formed in between roxithromycin and PEG 6000 in a given figure 4d obtained with the two different endothermic peaks at 57º C and 186ºC confirm their presence with melting point of both the component (roxithromycin and PEG 6000) with minor modification in their structure, this is because of formation of solid dispersion as the actual shift of endothermic peak was found with respect to thermogram of roxithromycin and PEG6000 which is earlier observed in figure 4a and 4b. One more endothermic peak was observed at 312º C in a figure 4d which is formed because of degradation of solid dispersion. Whereas in case of DSC thermogram of solid dispersion in between roxithromycin and HPMC observed with the two endothermic peak in a given figure 4e in which first peak observed at 80º C which is a very broad in size and confirm that the solid dispersion contain moisture, whereas another medium size endothermic peak at 298º confirm that the melting of roxithromycin and HPMC occur together as their melting point shifted after formation of solid dispersion.



(A)



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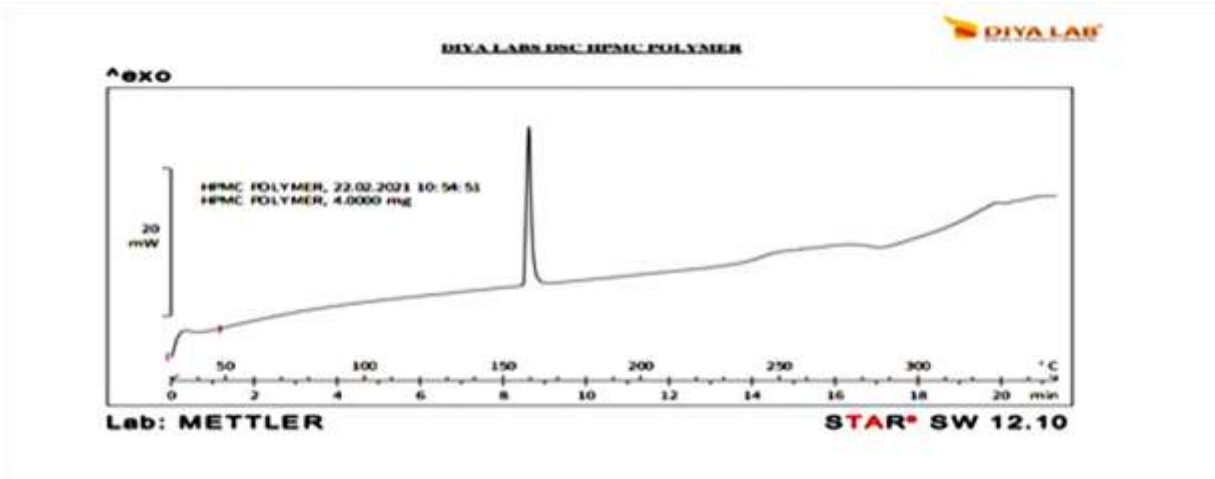

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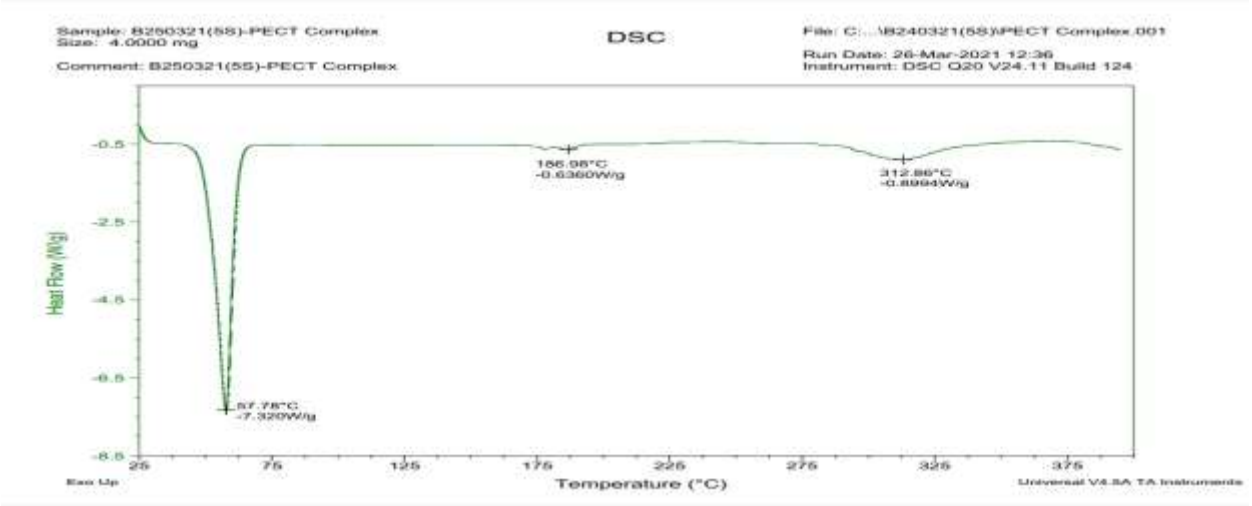
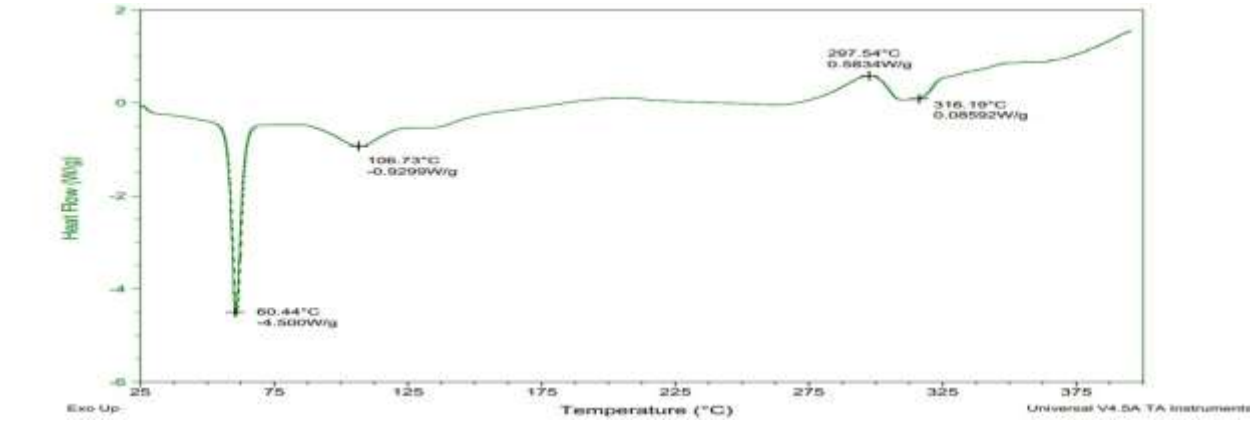


(D)



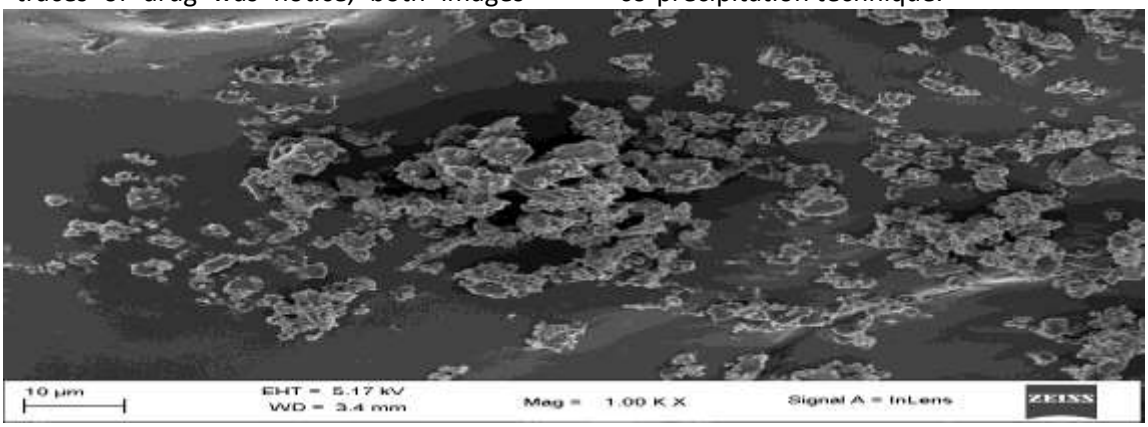
(E)

Fig. 4: Contain DSC thermogram of (A) Roxithromycin drug (B) PEG 6000 polymer (C) HPMC polymer (D) Solid dispersion of roxithromycin and PEG6000 (E) Solid dispersion ofroxithromycin and HPMC.

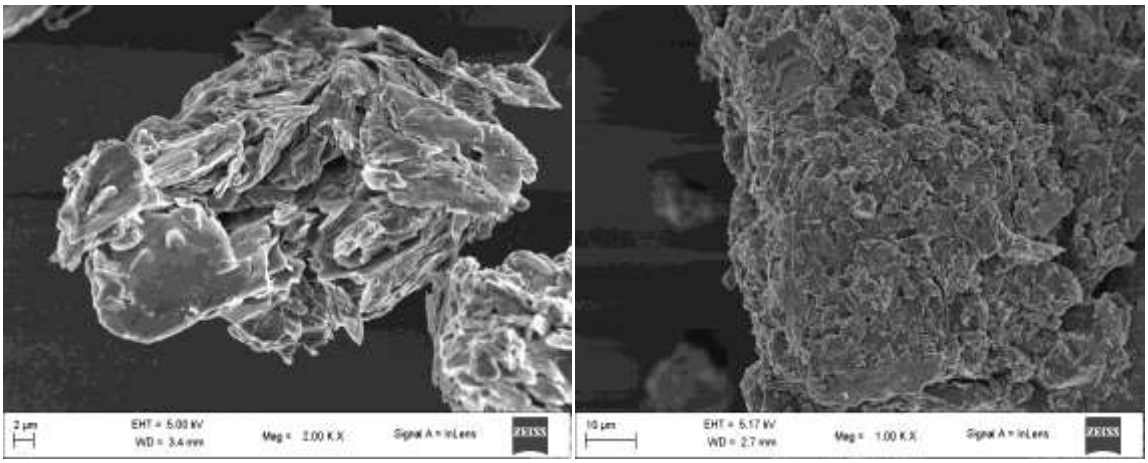
SEM

Scanning Electron Microscopy performed to detect the morphological variation in the

structure of the drug which occurs after formation of solid dispersion. Image of roxithromycin in figure 5a proved that drug have a irregular 3D crystals with smooth and oval corners, whereas both figures (in figure 5b and figure 5c) confirmed the formation of a new moiety called solid dispersion in which no traces of drug was notice, both images shows a 3-D amorphous heavy mass type structure, which formed because of the agglomeration in between drug and excipients. This kind of moiety without any drug traces confirmed the formation of new structure called solid dispersion with different characteristics which is formed after applying co-precipitation technique.



(A)



(B) **(C)**

Fig. 5: Contain SEM Images of (1) roxithromycin drug (2) Roxithromycin -HPMC solid dispersion and (3) Roxithromycin-PEG 6000 solid dispersion

Evaluation parameter of Complex

Determination of percent yield

Three batches of PEG 6000 and HPMC were prepared at a 1:0.5, 1:1, and 1:3 ratio under the same conditions to determine the percent yield of Roxithromycin, and the results were expressed as a mean standard deviation (mean S.D.) of 91.866±0.389 to 97.66±2.813 (range) percent yield.

Drug Content

In various Roxithromycin containing solid dispersions shows high amount of drug content. This indicated that the Roxithromycin is uniformly distributed in all these solid dispersions (3) (Saquib et al.) and highest drug content was shown by the HPMC in a ratio of 1:3 which was 93.381± 0.805.

In-vitro dissolution rate study

It was observed that, the formulation containing HPMC is SD-6 has shown highest

cumulative percent of Roxithromycin release is 93.381 in 1 hr compared to other formulations. Further pure Roxithromycin has shown only 33.927% of drug dissolved in water in one hour indicating that there was significant improvement in dissolution of Roxithromycin from dispersion prepared by the method called co-precipitated method. The increase in dissolution profile of Roxithromycin from solid dispersion may be due to reduction of particle size of the drug and increase wettability. Because of the tight contact between the drug and the hydrophilic polymer, the interfacial tension between the hydrophobic drug and the dissolution medium is reduced, allowing for better wetting and increased surface availability for dissolution.

Table 7: Evaluation Parameters of RXM- HPMC and RXM-PEG Complex

S. no.	Formulation Code	Drug: Polymer ratio	% Yield ±SD	%Drug Content ±SD	% Drug Dissolved ± SD
1	RXM: PG 0.5	1:0.5	93.466±0.830	81.79±0.036	73.335±0.430
2	RXM:PG 1	1:1	95.20±0.652	90.42±0.0005	83.553±0.308
3	RXM:PG 3	1:3	97.66±2.813	96.43±0.0006	90.972±0.411
4	RXM:HP 0.5	1:0.5	91.866±0.389	82.65±0.024	78.705±0.174
5	RXM:HP 1	1:1	92.80±0.652	91.32±0.038	87.075±0.479
6	RXM: HP 3	1:3	95.5±0.787	93.98±0.057	93.381±0.805

STABILITY STUDIES

The stability study for various Roxithromycin solid dispersions using only a 1:3 ratio of PEG 6000 and HPMC polymers was carried out for a time period of 6 months at different temperature points, with relative humidity (RH) of 40 ^{o}C± 2 ^{o}C and 75% ±5%. No significant difference in drug content and percent drug dissolved in 60 minutes was found in solid dispersion at different ratios were observed throughout the study.These observations of the stability study of various Roxithromycin solid dispersion using PEG6000 and HPMC at different ratios indicated no change in the state of solid dispersion during the study period indicating formulation is stable enough.

Table 8: Evaluation parameters for stability determination of RXM- HP3and RXM-PG3 complex

Evaluation Parameters	Time in days			
	0	30	45	60
Physical appearance RXM:PG 3	Crystalline irregular surface with dark grey color	***	***	***
Physical appearance RXM: HP 3	Amorphous irregular surface with brown color	***	***	***
% Drug Content RXM:PG 3	96.43±0.0006	95.85±0.02	95.42±0.015	94.70±0.010
% Drug Content RXM: HP 3	93.98±0.057	93.44±0.028	93.39±0.015	92.83±0.024
%Drug Dissolution RXM:PG 3	90.972±0.411	90.68±0.199	90.364±0.13	90.10±0.14
%Drug Dissolution RXM: HP 3	93.381±0.805	92.733±0.901	91.945±0.846	91.236±0.363

(*) Maintain same physical appearance.

CONCLUSION

Research that was concluded with success based on the dissolution, stability, and sustained effect enhancement of roxithromycin, in which several tests are done to support the result that was reached. Studies that were carried out using DSC and SEM gave proof that a complex evolved between them despite the fact that they did not interact with one another in any way. On the other hand, the initial dissolving rate of roxithromycin was enhanced with the help of solid dispersion's that were based on HPMC and PEG6000. This was achieved. In this particular instance, it was discovered that the formulation RXM HP3, which is a solid dispersion produced between roxithromycin and HPMC, had the highest rate of dissolving; on the other hand, RXM PG3 was shown to have the highest level of stability. RXM HP3 was determined to be the formulation that offered the highest overall performance and was selected as a result of the results relating its solubility and stability.

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