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Effect of Some Hydrophilic Polymers on Dissolution Rate of Roxithromycin

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In the present investigation, the enhancement of dissolution rate of roxithromycin was carried out by preparing solid dispersions using hydrophilic polymers like polyethylene glycol 6000, hydroxypropylmethylcellulose K4M and hydroxypropylcellulose, each in the ratios of 1:1, 1:3 and 1:5. Physical mixing and coprecipitate techniques were employed to prepare formulations for increasing the solubility of roxithromycin. Formulations prepared by both physical mixing and coprecipitate methods have shown significant enhancement of dissolution rates compared to pure roxithromycin alone. All the solid dispersions obtained were fine and having good flow properties. The formulation, polyethylene glycol 6000:CP_5 containing roxithromycin:polyethylene glycol 6000 in 1:5 ratio has shown 99.4% drug release in 1h. The dissolution rate of roxithromycin was directly proportional to the increment in the drug to polymer ratios in the solid dispersions. Dispersions prepared by coprecipitate method have shown faster dissolution rate compared to physical mixing techniques. The dissolution efficiency of the formulation polyethylene glycol 6000:CP_5 was found to be highest compared to other formulations. The release profiles of roxithromycin from the dispersions have followed first order release kinetics and Hixson-Crowell's cube root law. It was concluded that hydrophilic polymers can be employed to prepare solid dispersions to enhance the solubility of roxithromycin.

The enhancement of oral bioavailability of drugs with poor water solubility remains one of the most challenging aspects of drug development. Although salt formation, solubilization and particle size reduction have commonly been used to increase dissolution rate and there by oral absorption and bioavailability of such drugs, there are some practical limitations of these techniques. In case of salts, the increased dissolution rate in the gastrointestinal tract may not be achieved because of the reconversion of salts into aggregates of their respective acid or base forms. Further, solubilization of drugs in organic solvents or in aqueous media by the use of surfactants and cosolvents leads to liquid formulations that are usually undesirable from patient acceptability and commercialization. Particle size reduction is commonly used to increase dissolution rate and there is a practical limit to how much size reduction can be achieved by such commonly used methods as controlled crystallization and grinding[1,2].

In 1961, Sekiguchi and Obi[3] developed a practical method whereby many of the limitations associated with the enhancement of bioavailability of poorly water soluble drugs can be over come. This method, which was later termed solid dispersion[4], involves the formation of eutectic mixtures of drugs with water soluble carriers by the melting of their physical mixtures. Sekiguchi and Obi[2] suggested that the drug has present as a eutectic mixture in a microcrystalline state. Later it was demonstrated that all the drug in a solid dispersion might not necessarily be present in a microcrystalline state; a certain fraction of the drug might be molecularly dispersed in the matrix, thereby forming a

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solid solution. Solid dispersion is defined as dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by melting (fusion)[2], solvent[5] or melting-solvent method[6]. This technique provides a means of reducing particle size to nearly a molecular level. As the soluble carrier dissolves, the insoluble drug is exposed to dissolution medium as very fine particles for quick dissolution and absorption[7].

Chemically, roxithromycin (RXM), is erythromycin 9-[o-[(2)-methoxyethoxy)methyl] oxime, a semi synthetic macrolide antibiotic drug, very slightly soluble in water and aqueous fluids and its absorption is dissolution rate limited. RXM is used in the treatment of UTI, RTI, ENT, genital tract, skin and soft tissue infections[8]. In the present investigation several formulations of RXM were prepared employing physical mixture (PM) and coprecipitate (CP) methods using polymers like polyethylene glycol 6000 (PEG), hydroxypropylmethylcellulose K4M (HPMC) and hydroxypropylcellulose (HPC). The dissolution rates of the prepared formulations were studied and compared to those of pure RXM to evaluate the efficiency of solid dispersions in improving the dissolution rate.

MATERIALS AND METHODS

Roxithromycin was obtained as a gift sample from M/s Alkem Laboratories, Mumbai. Hydroxypropylmethylcellulose K4M and hydroxypropylcellulose were procured from Loba Chemie Ltd., Mumbai. Polyethylene glycol 6000 and methanol were purchased from SD Fine Chemicals Ltd., Boisar.

Solubility studies[9]:

Accurately weighed each samples (100 mg) of RXM were transferred to 50 ml conical flasks containing 10 ml aqueous solutions of each of the polymers in various concentrations (0.5,1.0,1.5, 2.0, 2.5 and 3.0% w/v). The flasks were closed with corks and shaken at room temperature up to 24 h using rotary shaker. The solutions were filtered through Whatman No.1 filter paper. The filtrates were diluted suitably with double distilled water and assayed for RXM at 207 nm[10] against double distilled water as blank. Formulations of RXM containing various drug-polymer ratios that were used to prepare physical mixtures and solid dispersions were shown in Table 1.

Preparation of physical mixtures:

Physical mixtures were prepared by thoroughly mixing accurately weighed quantities of RXM and polymers (PEG, HPMC and HPC) for five min in glass mortar individually. The powders were then sifted through mesh No. 120 and stored in a desiccator.

Preparation of solid dispersions:

Solid dispersions of RXM were prepared using PEG, HPMC and HPC in the ratios 1:1, 1:3 and 1:5 individually by coprecipipate method. The solvents employed to dissolve polymers for preparing solid dispersions were, methanol:dichloromethane (1:2) for HPMC and methanol alone for PEG and HPC to get the clear polymer solutions. To the solutions of polymers, weighed amounts of RXM were added into boiling test tubes individually. The solvents were then evaporated under vacuum at 70° and dried in a desic-

TABLE 1: FORMULATIONS OF RXM USING DIFFERENT METHODS

Method	RXM: Polymer (w/w)	Formulation code		
		PEG 6000	HPMC K4M	HPC
PM (Physical mixture)	1:1	$PEG\text{-}PM_1$	$HPM\text{-}PM_1$	$HPC\text{-}PM_1$
	1:3	$PEG\text{-}PM_3$	$HPM\text{-}PM_3$	$HPC\text{-}PM_3$
	1:5	$PEG\text{-}PM_5$	$HPM\text{-}PM_5$	$HPC\text{-}PM_5$
CP (Coprecipitate)	1:1	$PEG\text{-}CP_1$	$HPM\text{-}CP_1$	$HPC\text{-}CP_1$
	1:3	$PEG\text{-}CP_3$	$HPM\text{-}CP_3$	$HPC\text{-}CP_3$
	1:5	$PEG\text{-}CP_5$	$HPM\text{-}CP_5$	$HPC\text{-}CP_5$

Solid dispersions (coprecipitates, CP) and physical mixtures (PM) of roxithromycin (RXM) were prepared by using hydrophilic polymers such as PEG 6000, HPMC K4M and HPC in the RXM:polymer ratios 1:1, 1:3 and 1:5.

cator until the dry mixtures attain constant weights. The solidified masses were crushed, pulverized and passed through mesh No. 120. The flow properties of the prepared dispersions were determined by measuring angle of repose[11] and Carr's index[12].

Drug content estimation:

RXM content in physical mixtures and solid dispersions was estimated. Accurately weighed samples (10 mg) of the mixture were dissolved in 0.8 ml of methanol and volume was made up to 10 ml with double distilled water. This solution further suitably diluted with double distilled water and the absorbance was measured at 207 nm[10] using an Elico SL-159® UV/Vis spectrophotometer.

***In vitro* dissolution rate study:**

In vitro dissolution profiles of pure RXM, formulations of physical mixtures and solid dispersions of RXM were studied using USP XXI six stage dissolution rate test apparatus (# Tab-Machines®) employing paddle method. 900 ml of double distilled water was used as dissolution medium maintained at 37±0.5° and the stirrer rotation was kept at 50 rpm. Five millilitres of samples were withdrawn at different time intervals (5, 10, 20, 30, 40, 50 and 60 min) and the RXM content was assayed at 207 nm[10] using UV/Vis spectrophotometer. Cumulative percent RXM released vs. time plots were plotted. The dissolution efficiency (DE) of RXM in various formulations was calculated by the method proposed by Khan[13]. DE_{10}, DE_{30} and DE_{45} values were calculated from dissolution data.

Statistical analysis:

The reproducibility of the method was checked for all the prepared solid dispersions by preparing five bathes of the dispersions under similar set of the conditions and the percent yield of the dispersions was determined in different batches prepared. The results are expressed as mean±SD and subjected to analysis of variance (ANOVA) test to find out whether there is significant difference between the yields of the different bathes (Table 2).

Differential scanning calorimetry (DSC):

DSC thermograms of pure roxithromycin, PEG6000, HPMC K4M, HPC and selected dispersions (PEG-CP_5, HPM-CP_5 and HPC-CP_5) were determined by a differential scanning calorimeter (DSC 220C, Seiko, Japan) at a heating rate of 10°/min from 30 to 300° in nitrogen atmosphere.

RESULTS AND DISCUSSION

TABLE 2: PERCENTAGE YIELD OF RXM IN DIFFERENT BATCHES PREPARED

Formulation	Drug:Polymer	%Yield±S.D.
PEG-CP1	1:1	87.89±1.02
PEG-CP3	1:3	86.17±0.87
PEG-CP5	1:5	87.90±1.33
HPM-CP1	1:1	88.02±1.22
HPM-CP3	1:3	86.69±0.81
HPM-CP5	1:5	88.12±1.14
HPC-CP1	1:1	88.42±0.47
HPC-CP3	1:3	86.50±0.52
HPC-CP5	1:5	88.14±1.13

Percentage yield of the preparations were determined by preparing five batches under similar set of conditions to check the reproducibility of the method and expressed as mean±SD.

Solubility studies of RXM were carried out in various polymer solutions at different concentrations. The results have shown that solubility of RXM in double distilled water was 5.54 µg/ml. The solubility of RXM was found to be directly proportional to the increment in the concentration of polymers from 0.5-3% in the polymer solutions. The solubility of RXM in the polymer solutions was in the order of PEG>HPMC>HPC (Table 3). The values of angle of repose (25-29°) and Carr's index (14-17%) given in the Table 4 indicated that all formulations of RXM prepared by coprecipitate method were fine and having good flow properties.

The DSC scans of pure drug, PEG, HPMC, HPC and solid dispersions are presented in the fig. 1. The melting

TABLE 3: SOLUBILITY OF RXM IN VARIOUS CARRIERS

Concentration of	Solubility (µg/ml) in various carriers		
Carrier (%)	HPC	HPMC K4M	PEG 6000
0.5	6.12	6.84	7.35
1	6.74	7.15	8.52
1.5	7.15	9.34	10.6
2	8.36	11.6	14.8
2.5	10.2	12.7	18.3
3	13.8	15.8	24.7

Solubility of roxithromycin in various concentrations of three carriers was determined triplicate (n=3) by phase solubility studies. Excess amount of the RXM was added to the aqueous carrier solution, shaken for 24 h and the filtrates were assayed for RXM at 207 nm.

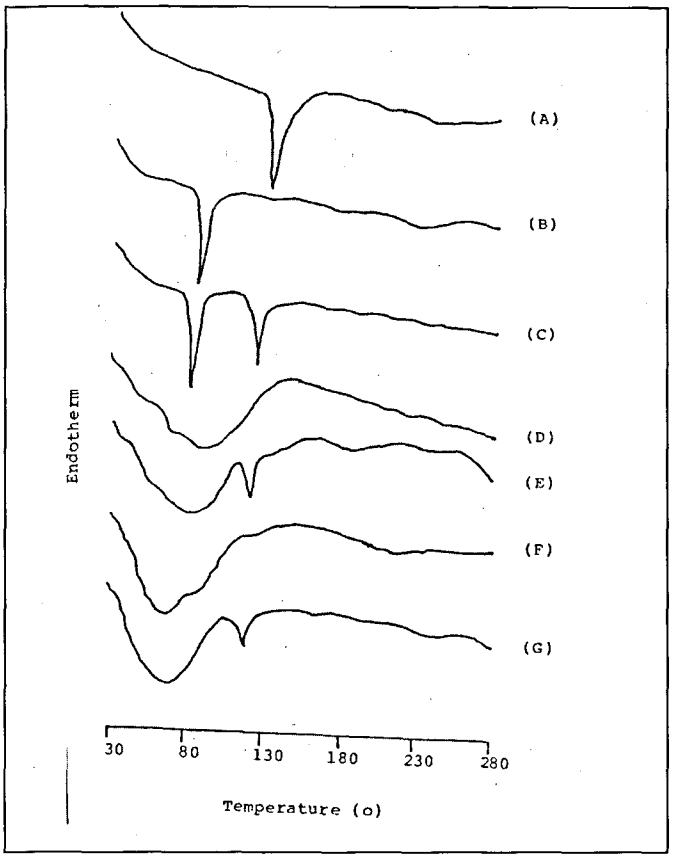

Fig. 1: DSC thermograms of solid dispersions of roxithromycin

Differential scanning calorimetric thermograms of A) pure roxithromycin, B) PEG 6000, C) solid dispersion (1:5, drug:PEG), D) HPMC K4M, E) solid dispersion (1:5, drug:HPMC), F) HPC and G) solid dispersion (1:5, drug:HPC) were taken to determine any interaction between the drug and carrier.

endotherms of pure roxithromycin and PEG alone gave peaks at 125° and 60° respectively corresponding to their melting points, where as HPMC and HPC showed broad peaks at 55° and 75° may be due to dehydration. Solid dispersion of roxithromycin and PEG showed same peaks at temperatures corresponding to the pure compounds indicating no interaction of the carrier with the drug in the dispersed state. In the case of HPMC and HPC solid dispersions, the intensity of peak corresponding to roxithromycin was decreased though the thermogram showed two peaks corresponding to the melting points of pure compounds. This may be due to low drug level in the dispersion or complete miscibility of the drug within the carrier polymer.

Dissolution profiles of RXM from physical mixtures and solid dispersions were compared with those of pure RXM (figs. 2-4). All the formulations of physical mixtures and solid dispersions have shown significant increase in the release rate of RXM compared to pure drug. Dissolution rates of RXM were increased with the increment in polymer concentrations in the drug polymer ratios as shown in Table 3. The increment in the dissolution rate of different formulations was found to be in the order of PEG>HPMC>HPC (fig. 5).

It was observed that, the formulation PEG-CP_5, prepared by coprecipitate method has shown highest cumulative percent of RXM release of 99.4% in 1 h compared to other formulations. Further pure RXM has shown only 39.5% dissolution in 1 h indicating that there was significant improvement in dissolution of RXM from dispersions prepared by above method (Table 5). The increase in dissolution profile of RXM from solid dispersions may be due to reduction of particle size of the drug and increased wettability. In the case of physical mixtures, increased dissolution rate of RXM may be due to surface tension lowering effect of carriers resulting in wetting of hydrophobic RXM surface[14].

Low values of standard deviation in respect of drug content (Table 4) indicated that the drug was uniformly distributed in all the solid dispersions. The ANOVA test performed among the percent yield of the different batches confirmed that there was no significant difference at $P<0.05$ among the formulations prepared. Hence the method used to prepare the dispersions was found to be reproducible.

TABLE 4: ANGLE OF REPOSE AND CARR'S INDEX OF PREPARED DISPERSIONS

Formulation	Drug: Polymer	Angle of Repose	Carr's Index
PEG-CP1	1:1	27.58±0.73	14.25±1.26
PEG-CP3	1:3	25.64±0.11	15.75±0.94
PEG-CP5	1:5	28.15±0.28	16.12±0.63
HPM-CP1	1:1	28.42±0.55	15.98±1.12
HPM-CP3	1:3	26.32±0.96	13.38±0.87
HPM-CP5	1:5	26.74±0.75	14.16±1.24
HPC-CP1	1:1	25.28±0.84	15.32±0.48
HPC-CP3	1:3	28.65±0.72	14.82±0.57
HPC-CP5	1:5	28.87±0.95	14.56±1.66

Angle of repose of the prepared solid dispersions was determined by fixed-base method and Carr's index was calculated from the bulk and tapped density and expressed as mean±SD (n=5)

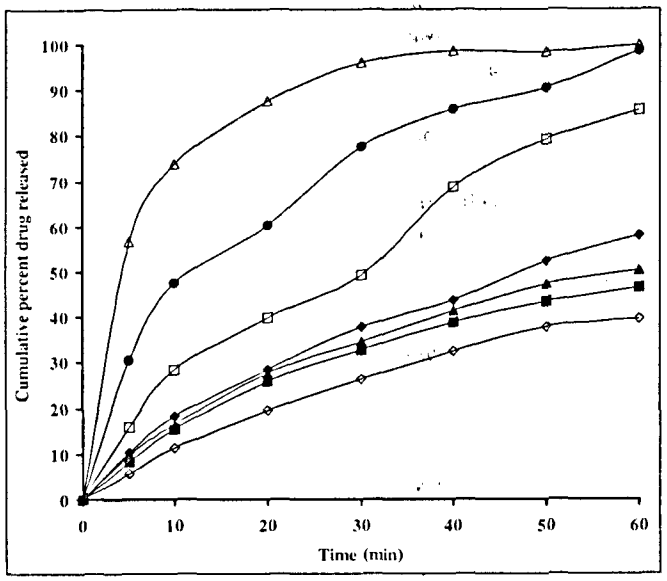

Fig. 2: Dissolution profiles of RXM from PEG formulations

***In vitro* dissolution profiles of RXM from PEG formulations showing pure drug (-◇-),PEG-PM_1 (-▫-), PEG-PM_3 (-▲-), PEG-PM_5 (-◆-), PEG-CP_1 (-□-), PEG-CP_3 (-●-) and PEG-CP_5 (-△-) were studied in 900 ml of double distilled water, samples drawn at regular time intervals and roxithromycin content was measured spectrophotometrically at 207 nm.**

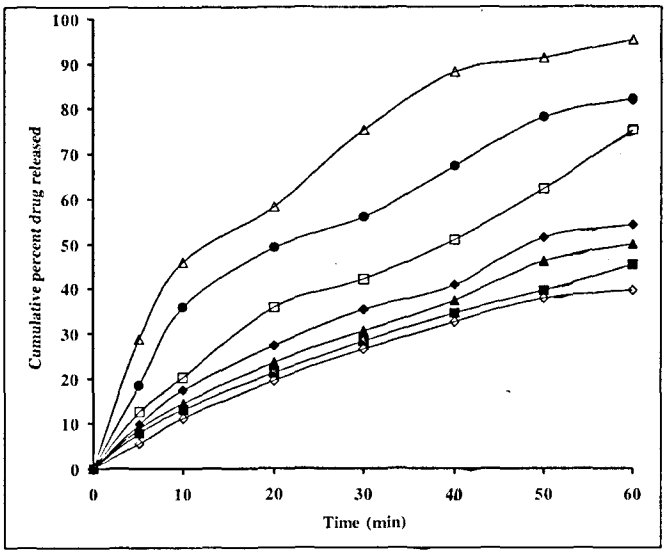

Fig. 3: Dissolution profiles of RXM from HPMC formulations

***In vitro* dissolution profiles of RXM from HPMC formulations showing pure drug (-◇-), HPM-PM_1 (-▫-), HPM-PM_3 (-▲-), HPM-PM_5 (-◆-), HPM-CP_1 (-□-), HPM-CP_3 (-●-) and HPM-CP_5 (-△-) were studied in 900 ml of double distilled water, samples drawn at regular time intervals and roxithromycin content was measured spectrophotometrically at 207 nm.**

The RXM release profiles from the formulations prepared by physical mixing and coprecipitate methods were compared. The release rate of RXM from the formulations using the above methods was found to be in the order of coprecipitate>physical mixing>pure RXM.

Dissolution rates of RXM from physical mixtures and solid dispersions followed first order kinetics[15,16] (Table 5). Hixson-Crowell's cube root law[17] states that powder of uniform particle size dissolving under sink conditions given as, $W_0^{1/3}-W^{1/3}=K_{HC}t$, where, W_0 is the initial amount of drug in the dosage form, W is the remaining amount of drug at time t and K_{HC} is the release rate constant for Hixson-Crowell rate equation. This law describes the release from systems where there is a change in surface area and diameter of the particles. As all formulations have shown significant increase in the Hixson-Crowell's cube root constant compared to pure RXM, it was assumed that they have followed Hixson-Crowell's cube root law (Table 5). The correlation coefficient (r) values of the first order release model are found to be (0.9840-0.9995) slightly higher when compared to the Hixson-Crowell's cube root model. Hence the release of the drug from the preparations followed predominantly first order kinetics compared to Hixson-Crowell cube root law. As the amount of carriers increased in the formulations, T_{50} (time for dissolution of 50% of drug) values were decreased significantly with all the three polymers indicating that there was improvement in dissolution rates of RXM (Table 5).

Dissolution efficiency (DE) is defined as the area under the dissolution curve up to the time t expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time[13]. Dissolution Efficiency (DE) = $\left(\frac{\int y\,dt}{y_{100}t}\right)100$ where, DE was calculated for pure RXM and all formulations of RXM at 10, 30 and 45 min and the results were summarized in Table 6. As the dissolution time increased from 10 to 45 min, the DE was increased. Among the formulations, PEG:CP_5 has shown maximum dissolution efficiencies of 46.8, 63.0 and 70.3 % at DE_{10}, DE_{30} and DE_{45}, respectively.

The above discussion indicates that dissolution rate of RXM can be enhanced by formulating dispersions of RXM using physical mixing and coprecipitate techniques. Be-

TABLE 5: COMPARISON OF VARIOUS PARAMETERS OF RXM WITH VARIOUS FORMULATIONS

Formulation	Drug: Polymer	% drug content ±SD	% drug dissolved/h ±SD	Dissolution rate Constant (min^{-1})	Hixson-Crowell's cube root constant ($mg^{1/3}/min$)	T_{50} (min)
Pure RXM	-	-	39.5±0.20	0.008	0.026	86.6
PEG-CP_1	1:1	94 ±0.2	85.4±0.32	0.031	0.081	22.4
PEG-CP_3	1:3	92 ±0.5	98.4±0.36	0.060	0.093	11.6
PEG-CP_5	1:5	94 ±0.4	99.4±0.36	0.084	0.114	8.25
PEG-PM_1	1:1	89 ±0.6	46.4±0.10	0.001	0.031	72.2
PEG-PM_3	1:3	97 ±0.2	50.3±0.25	0.011	0.035	63.0
PEG-PM_5	1:5	93 ±0.5	57.8±0.25	0.013	0.040	53.3
HPM-CP_1	1:1	91 ±0.4	75.3±0.30	0.019	0.059	35.9
HPM-CP_3	1:3	96 ±0.8	82.6±0.40	0.026	0.069	26.7
HPM-CP_5	1:5	89 ±1.1	95.2±0.20	0.049	0.104	14.1
HPM-PM_1	1:1	92 ±0.8	45.4±0.20	0.009	0.029	75.3
HPM-PM_3	1:3	95 ±0.4	49.1±0.96	0.011	0.034	63.0
HPM-PM_5	1:5	93 ±0.2	54.2±0.25	0.012	0.036	56.8
HPC-CP_1	1:1	92 ±0.4	57.5±0.20	0.014	0.042	50.2
HPC-CP_3	1:3	93 ±0.4	68.5±0.20	0.018	0.046	38.7
HPC-CP_5	1:5	93 ±0.2	82.2±0.25	0.026	0.069	26.7
HPC-PM_1	1:1	95 ±0.4	43.6±0.30	0.008	0.027	81.5
HPC-PM_3	1:3	91 ±0.2	48.2±0.25	0.010	0.032	69.3
HPC-PM_5	1:5	93 ±0.2	52.2±0.10	0.012	0.035	60.3

Drug contents of preparations were determined (n=3) by dissolving weighed quantities in minimum amount of methanol, the volume was made up with double distilled water and assayed for drug at 207 nm. Percent drug dissolved, dissolution rate constants and T_{50} were determined from dissolution studies conducted (n=3) with 900 ml of double distilled water. T_{50} is the time at which 50% of the drug release occurs. Hixson-Crowell's cube root constant is determined from the plots of the cube root of the drug released versus time.

tween the two methods used, dispersions prepared by coprecipitate method were satisfactory and have shown significant improvement in dissolution profiles of RXM compared to those prepared by physical mixing technique. The formulation, PEG:CP_5 containing RXM:PEG in 1:5 ratio, has shown highest dissolution rate of 99.4% in 1 h compared to formulations prepared by using other polymers. Dissolution rate of RXM has followed first order kinetics and Hixson-Crowell's cube root law. Therefore it was concluded that hydrophilic polymers like PEG, HPMC and HPC could be used as carriers to prepare solid dispersions to enhance the dissolution rate of RXM significantly. PEG can be used as a suitable carrier for enhancing dissolution rate of RXM. This study unveils scope for further evaluation on the usage of hydrophilic polymers as carriers to prepare solid dispersions to enhance the solubility of RXM.

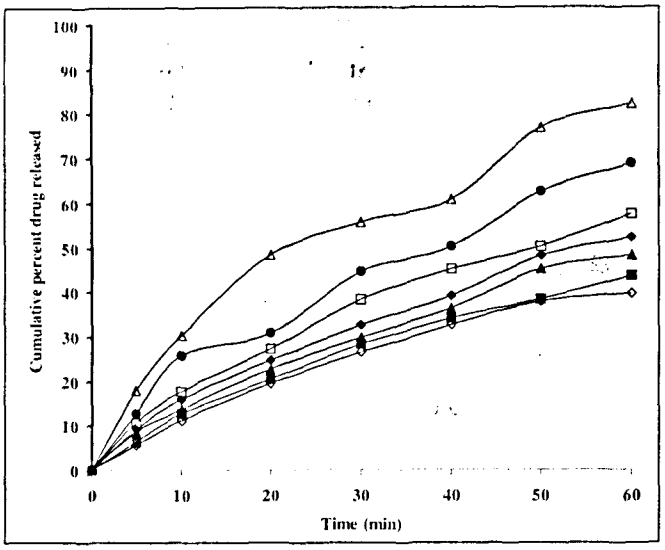

Fig. 4: Dissolution profiles of RXM from HPC formulations

***In vitro* dissolution profiles of RXM from HPC formulations showing pure drug (-◇-) HPC-PM_1 (-▫-), HPC-PM_3 (-▲-), HPC-PM_5 (-◆-), HPC-CP_1 (-□-), HPC-CP_3 (-●-) and HPC-CP_5 (-△-) were studied in 900 ml of double distilled water, samples drawn at regular time intervals and roxithromycin content was measured spectrophotometrically at 207 nm.**

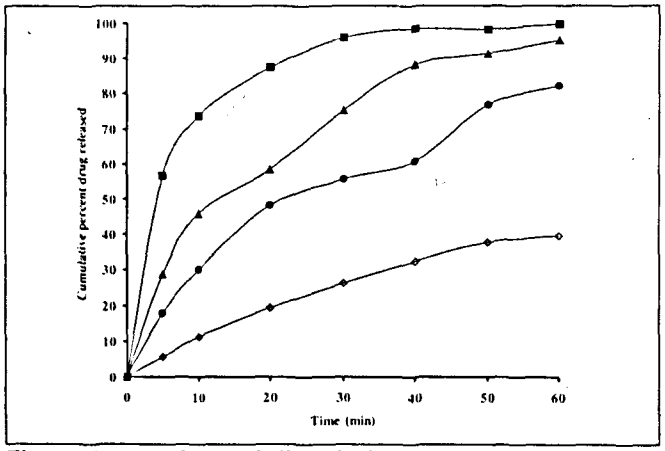

Fig. 5: Comparison of dissolution profiles of RXM from different polymers

Comparison of *in vitro* dissolution profiles of RXM from different polymers at RXM:polymer (1:5) ratio showing pure drug (-◇-), PEG-CP_5 (-▫-), HPM-CP_5 (-▲-) and HPC-CP_5 (-●-), among the three polymers used, PEG 6000 showed highest dissolution rate.

TABLE 6: DISOLUTION EFFICIENCY OF RXM IN VARIOUS FORMULATIONS

Formulation	Drug: Polymer	Dissolution efficiency (%)		
		DE_{10}	DE_{30}	DE_{45}
Pure RXM	-	5.60	14.6	16.3
PEG-CP_1	1:1	14.9	31.1	38.9
PEG-CP_3	1:3	27.0	49.9	51.4
PEG-CP_5	1:5	16.8	73.0	70.3
PEG-PM_1	1:1	7.93	19.2	20.7
PEG-PM_3	1:3	8.20	18.8	20.8
PEG-PM_5	1:5	9.70	22.0	23.7
HPM-CP_1	1:1	11.3	26.1	27.7
HPM-CP_3	1:3	18.2	37.7	38.8
HPM-CP_5	1:5	25.8	48.2	50.3
HPM-PM_1	1:1	6.45	14.7	16.2
HPM-PM_3	1:3	7.83	15.6	17.0
HPM-PM_5	1:5	11.4	21.8	23.6
HPC-CP_1	1:1	8.15	19.3	21.5
HPC-CP_3	1:3	12.7	24.7	26.1
HPC-CP_5	1:5	16.5	35.9	36.9
HPC-PM_1	1:1	7.03	12.9	14.2
HPC-PM_3	1:3	8.35	15.9	16.9
HPC-PM_5	1:5	9.12	20.0	22.1

Dissolution efficiency (DE) values of the prepared formulations at time 10, 30 and 45 min were determined from the area under the dissolution curve up to the time t.

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REFERENCES

1. Wadke, D.A., Serajuddin, A.T.M., and Jacobson, H., In; Preformulation Testing in Pharmaceutical Dosage Forms: Tablets, Vol 1, Marcel Dekker Inc., New York, 1989, 1.
2. Serajuddin, A.T.M., **J. Pharm. Sci**, 1999, 88, 1058.
3. Sekiguchi, K. and Obi, N., **Chem. Pharm. Bull.**, 1961, 9, 866.
4. Chiou, W.L. and Riegelman, S., **J. Pharm. Sci.**, 1971, 60, 1281.
5. Tachibana, T. and Nakamura, A., **Kolloid. Z. Polym**. 1965, 203, 130.
6. Chiou, W.L. and Smith, L.D., **J. Pharm. Sci.**, 1971, 60, 125.
7. Corrigan, O.I., **Drug Develop. Ind. Pharm.**, 1985, 11, 697.
8. Reynolds, J.E.F., Eds., In.; Martindale The Extra Pharmacopoeia, 31st Edn., Royal Pharmaceutical Society, London, 1996, 272.
9. Higuchi, T. and Connors, K.A., **Adv. Anal. Chem. Instr.**, 1965, 4, 117.
10. Sradhanjali, P., Himasankar, K., Rao, M.E.B. and Prakash, K., **Acta Ciencia Indica.**, 2003, 3, 195.

11. Parrot, E.L., In: Lachman, L., Lieberman, H.A. and Kanig, J.L., Eds., The Theory and Practice of Industrial Pharmacy, 3rd Edn (Indian), Varghese Publishing House, Bombay, 1987, 67.
12. Carr, R.L., **Chem. Engng. Jpn.,** 1965, 18, 163.
13. Khan, K.A., **J. Pharm. Pharmacol.,** 1975, 27, 48.
14. Sekikawa, H., Nakano, M. and Arita, T., **Chem. Pharm. Bull.,** 1979, 27, 1223.
15. Wagner, J.G., **J. Pharm. Sci.,** 1969, 58, 1253.
16. Gibaldi, M. and Feldman, S., **J. Pharm. Sci.,** 1967, 56, 1268.
17. Hixson, A.W. and Crowell, J.H., **Ind. Eng. Chem.,** 1931, 23, 923.