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Solubility and Stability Enhancement of Poorly-Soluble Drugs Clarithromycin and Prednisolone by Combination with Other Drugs

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Abstract: An attempt has been made to enhance the solubility and stability of two poorly-soluble drugs, clarithromycin and prednisolone by forming their combinations with three widely consumed non-prescription drugs: paracetamol, caffeine and ibuprofen. For solubility enhancement, three methods; Solution phase studies, solid dispersions and physical mixtures were used. It is seen that paracetamol produced significant enhancement in solubility of both clarithromycin and prednisolone by all the three methods. A comparison of different methods showed that solid dispersion method produced maximum enhancement for both the drugs. However, as compared to clarithromycin, the magnitude of enhancement was smaller in the case of prednisolone. With increase in ionic strength of the medium, a small decrease in solubility was observed in each case. Paracetamol was also found to be most effective combination drug in enhancing the stability of clarithromycin as well as prednisolone.

Key words: Solubility, stability, combinations, clarithromycin, prednisolone

INTRODUCTION

Solubility and stability issues are two major formulation obstacles hindering the development of therapeutic agents (Cappello *et al*., 2006; Yang *et al*., 2007). Although a number of solubilizing and stabilizing agents are available, each of these has a number of significant disadvantages (Nuijen *et al*., 2001; Yalkowsky *et al*., 1998). The idea of combining two or more drugs with complementary mode of action is to produce additivity of the desired therapeutic effect, but not of the side effects (Tallaride *et al*., 1997). Combination Therapy also plays an important role in the development of improved drug delivery devices (Ammar *et al*., 1997; Lim and Go, 2000).

Clarithromycin (6-O-methylerythromycin), is a semi-synthetic macrolide antibiotic and prednisolone is a synthetic adrenal corticosteroid with potent anti-inflammatory properties. Both the drugs exhibit poor aqueous solubility. Solubility enhancement has broad implications in the delivery of poorly-soluble drugs (Zhao *et al*., 1999; Strickley, 2004; Millard *et al*., 2002). Potential absorption problems occur if the aqueous solubility of a drug is less than 1 mg mL^{-1}. Stability studies are important since drug degradation not only leads to decrease in the therapeutic activity, it may also result in the appearance of a toxic degradation product upon storage of formulation (Carstensen, 1990). Yonemochi *et al*. (1999) have studied the physico-chemical properties of amorphous clarithromycin produced by grinding and spray drying. Cyclodextrin-complexation and liposome-encapsulation are some of the other approaches reported in the literature for solubility enhancement of clarithromycin (Salem and Duzqunes, 2003). Increase in the solubility of prednisolone in the presence of gelatin has been reported (Kallinteri and Antimisiaris, 2001). In this work efforts have been made to enhance the solubility and stability of poorly-soluble drugs, clarithromycin and prednisolone by combination with widely consumed non-prescription drugs: paracetamol, caffeine and ibuprofen.

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MATERIALS AND METHODS

The study was conducted at the Department of Chemistry, Panjab University, Chandigarh, India during the year 2006. Clarithromycin, prednisolone, caffeine, paracetamol and ibuprofen were obtained as gift samples from various manufacturers. All other reagents were of analytical grade and were used without further purification. Water used was double distilled in an all glass apparatus. 0.1 M phosphate buffer (pH 7.4) was prepared by mixing 19 mL of 0.2 M NaH_2PO_4 with 81 mL of 0.2 M Na_2HPO_4 and diluting the mixture to 200 mL with water.

Drug Analysis

Estimation of clarithromycin was based on the formation of a red colored chromogen with ferric chloride and 1,10-phenanthroline (Reddy *et al*., 2003; Sivasubramanian *et al*., 2004). Three hundred μM stock solution of clarithromycin was prepared in standard 0.1 M HCl. Five dilutions of the drug stock solution in the concentration range 10-300 μM were used for analysis. Three milliliter aliquot of each standard drug solution was mixed with 1.5 mL of ferric chloride (0.033 M) and 1.5 mL of 1,10 phenanthroline (0.1 M). The solutions were maintained at 40°C for 15 min. They were then cooled and 1 mL of ortho-phosphoric acid was added to each solution. The absorbance of the red colored chromogen was measured at 510 nm against a reagent blank. The absorbance of the reaction mixture remained stable for 4 h. The extinction coefficients, obtained from the absorbance versus drug concentration plots were used for drug estimation. Prednisolone could be analyzed directly by preparing standard drug solutions in phosphate buffer (pH 7.4) and using ultraviolet absorption spectrophotometric method for drug analysis.

Solubility Enhancement

An attempt has been made to enhance the solubility of clarithromycin and prednisolone by forming their combinations with paracetamol, caffeine and ibuprofen, using the following three methods: i) Solution phase studies, ii) Solid dispersions, iii) Physical mixtures.

Solution Phase Studies

0.1 g portions of clarithromycin/prednisolone, taken in sealed conical flasks, were mixed with 10 mL portions of combination drug (caffeine, paracetamol, ibuprofen) solutions of increasing concentrations prepared in 0.1 M phosphate buffer (pH 7.4). The mixture was stirred on a magnetic stirrer at 25°C for 24 h. Preliminary experiments showed that this time interval was sufficient for attainment of equilibrium. The solutions were filtered through 0.45 μm filter and the clarithromycin concentration in the filtrate was determined spectrophotometrically after appropriate dilution. The concentration range for combination drugs was 50-4000 μM in the case of caffeine, 50-200 μM in the case of paracetamol and 50-500 μM in the case of ibuprofen. The concentration range was lower in the case of paracetamol and ibuprofen, due to the limited solubility of these drugs in phosphate buffer.

Solid Dispersions

For preparation of solid-dispersions, 0.05 g of clarithromycin/prednisolone and 0.05 g of the combination drug were dissolved in 5 mL of chloroform, the contents were stirred for 1 h and the solvent was evaporated at 40°C using rotary vacuum evaporator. The solubility of clarithromycin/prednisolone in the solid dispersion was determined, as described earlier.

Physical Mixtures

For preparation of physical mixtures, equal weights of two drugs were taken in a passel mortar and thoroughly mixed. The mixture was used for solubility determination in the same way as described earlier.

Effect of Ionic Strength on Solubility

To study the effect of ionic strength on solubility, the data in solution phase was also obtained in the presence of 0.15 M NaCl. All other conditions were same.

Stability Studies

For stability studies, drug solutions were kept at room temperature in dark. The amount of drug degraded and drug remaining was determined spectrophotometrically at different time intervals for a period of 42 days. Single drugs as well as their combinations were studied. The final concentration of clarithromycin/prednisolone as well as the combination drugs was 100 μM in each case. The solvent used was 0.1 N HCl in case of clarithromycin and its combinations and phosphate buffer (pH 7.4) in the case of prednisolone and its combinations.

RESULTS AND DISCUSSION

An attempt has been made to enhance the solubility and stability of poorly soluble drugs, clarithromycin and prednisolone by forming their combinations with three non-prescription drugs: paracetamol, caffeine and ibuprofen.

Solubility Enhancement

For solubility enhancement, three methods; Solution phase studies, solid dispersions and physical mixtures were used.

Solution Phase Studies

Clarithromycin-drug Combinations

Solubility of clarithromycin alone and in the presence of increasing concentrations of caffeine (50-4000 μM), paracetamol (50-2000 μM) and ibuprofen (50-500 μM) was determined at 25°C in phosphate buffer (pH 7.4). The maximum drug concentration used was lower in the case of paracetamol and ibuprofen due to the limited solubility of these drugs in phosphate buffer. It was found that all the three drugs, caffeine, paracetamol and ibuprofen enhanced the solubility of clarithromycin. Solubility was found to increase with increase in the concentration of combination drug in each case. Significant enhancement in solubility of clarithromycin was observed in the case of paracetamol. The increase was relatively smaller in the case of caffeine and least in case of ibuprofen. As compared to clarithromycin only, the solubility could be enhanced by 20.3, 4.74 and 1.156 times in the case of paracetamol, caffeine and ibuprofen, respectively (Fig. 1, 2).

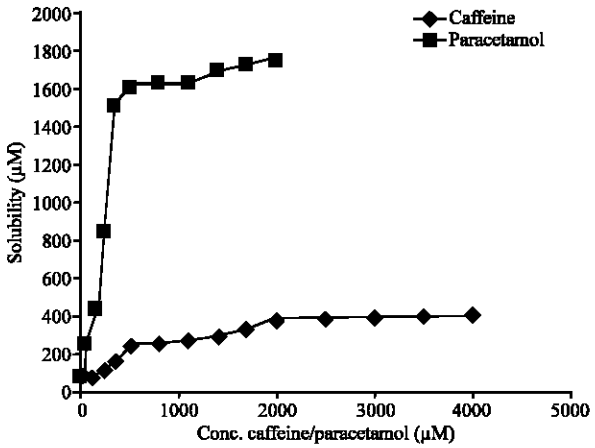

Fig. 1: Solubility of clarithromycin in the presence of caffeine and paracetamol

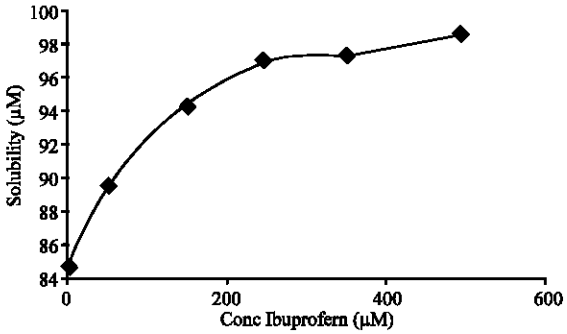

Fig. 2: Solubility of clarithromycin in the presence of ibuprofen

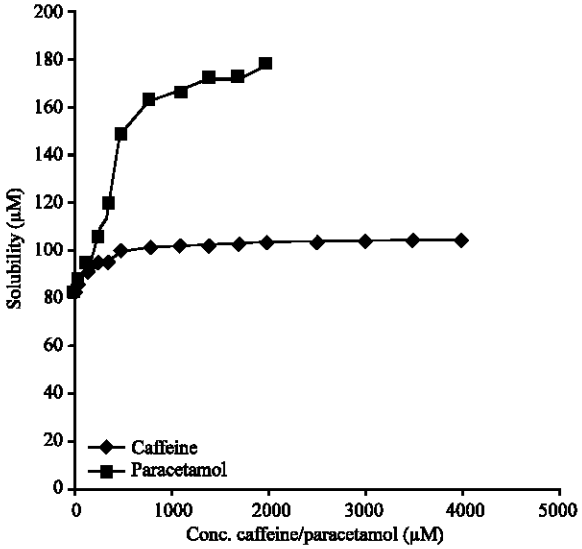

Fig. 3: Solubility of prednisolone in the presence of caffeine and paracetamol

The solubilization efficiency of a solvent should be a function of the relative magnitudes of the solute-solvent and various inter- and intra-molecular solvent-solvent interactions. Since clarithromycin as well as the combination drugs used, contain a large number of hydrogen bond donors and acceptors, hydrogen bonding interactions between clarithromycin and the combination drugs appear to be responsible for the enhancement of aqueous solubility of clarithromycin. The solubility increase in each case was significant up to an optimum concentration of the combination drug required for hydrogen bond formation. For example, in the case of paracetamol, solubility enhancement was significant only up to 500 µM concentration.

Prednisolone-drug Combinations

Solubility of prednisolone alone and in the presence of increasing concentrations of caffeine, paracetamol and ibuprofen was determined at 25°C in phosphate buffer (pH 7.4) (Fig. 3, 4). Solubility was found to increase with increase in the concentration of combination drug. All the drugs, caffeine, paracetamol and ibuprofen enhanced the solubility of prednisolone. Again maximum solubility enhancement was observed in case of paracetamol and least in case of ibuprofen. As compared to prednisolone only, the solubility could be enhanced by 2.149, 1.27 and 1.018 times in case of

Table 1: Solubility of clarithromycin and prednisolone in solid dispersion with other drugs

	Solubility (μM)		
Type of combination	Solution phase*	Solid dispersion	Physical mixture
Clarithromycin only	85.00	-	-
Clarithromycin-Caffeine	401.12	615.14	413.29
Clarithromycin-Paracetamol	1731.12	1835.06	1510.12
Clarithromycin-Ibuprofen	98.012	-	96.204
Prednisolone only	82.08	-	-
Prednisolone-Caffeine	103.02	178.18	173.52
Prednisolone-Paracetamol	176.40	256.45	217.25
Prednisolone-Ibuprofen	83.62	-	119.40

*Reported solution phase values are at the highest drug concentration

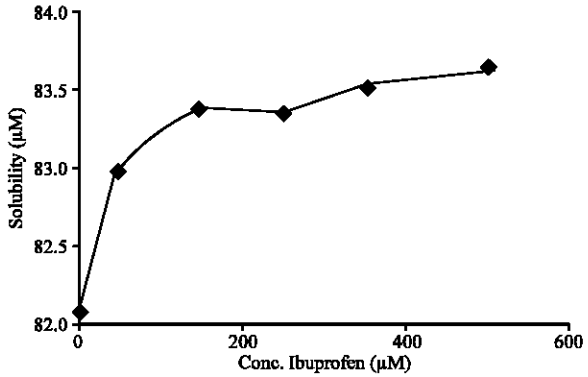

Fig. 4: Solubility of prednisolone in the presence of ibuprofen

paracetamol, caffeine and ibuprofen, respectively. Thus, solubility enhancement was lesser in the case of prednisolone as compared to clarithromycin

Solid Dispersion

An attempt has also been made to enhance the solubility of clarithromycin and prednisolone by preparing solid dispersions of the drug with caffeine and prednisolone in 1:1 weight ratio. Solid dispersion could not be prepared in the presence of ibuprofen since a gelly like mass was obtained after the evaporation of solvent It was found that the solubility of clarithromycin increased from 85 to 615 μM (7.2 times) in the case of clarithromycin-caffeine combination and 85 to 1835 μM (21.6 times) in the case of clarithromycin-paracetamol combination. The solubility of prednisolone increased from 82.08 μM 178.18 μM (2.17 times) in the case of prednisolone-caffeine combination and from 82.08 μM to 256.45 μM (3.12 times) in the case of prednisolone-paracetamol combination (Table 1).

Physical Mixtures

The solubility of clarithromycin and prednisolone in physical mixtures with the combination drugs, caffeine, paracetamol and ibuprofen was also determined at 25°C in phosphate buffer (pH 7.4). The solubility enhancement data is given in Table 1.

Comparison of the Three Methods

The solubility of clarithromycin and prdnisolone in the absence and presence of combination drugs using the three methods has been compared. It is seen (Table 1) that paracetamol produced significant enhancement in solubility of both clarithromycin and prednisolone by all the three methods. A

Table 2: Effect of ionic strength on the solubility of poorly soluble drugs

Type of combination	Conc. of combination drug (μM)	Solubility (μM)	
		Buffer without NaCl	Buffer with NaCl
Clarithromycin-Caffeine	4000	403.12	368.45
Clarithromycin-Paracetamol	2000	1732.14	1612.29
Clarithromycin-Ibuprofen	500	98.296	94.32
Prednisolone-Caffeine	4000	104.28	103.14
Prednisolone-Paracetamol	2000	176.40	172.46
Prednisolone-Ibuprofen	500	83.62	81.29

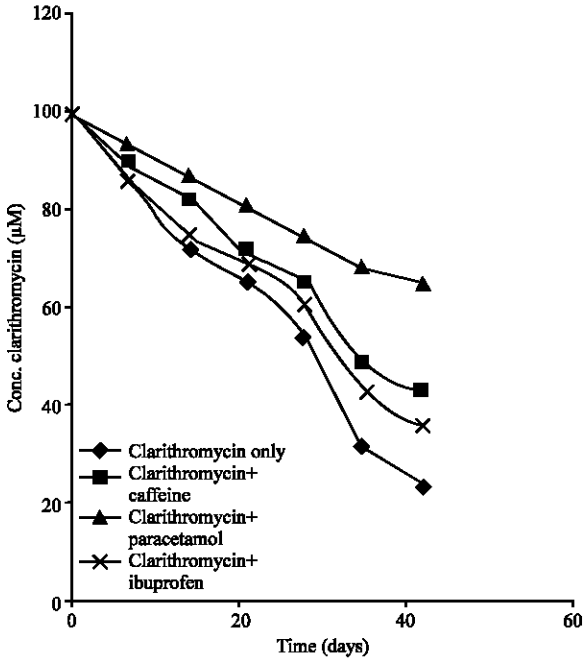

Fig. 5: Degradation of clarithromycin in the absence and presence of combination drugs

comparison of different methods showed that solid dispersion method produced maximum enhancement for both the drugs. However, as compared to clarithromycin, the magnitude of enhancement was smaller in the case of prednisolone.

Effect of Ionic Strength

The solubility of clarithromycin and prednisolone was also studied in solution phase in the absence and presence of 0.15 M NaCl. A small decrease in the solubility of the drug combination in the presence of sodium chloride appears to be a characteristic of the 'salting out' phenomenon. With increase in ionic strength, more salt would be competing with the solute for water molecules and this would effectively reduce the solubility of the dissolved material (Table 2).

Enhancement of Stability

Stability of clarithromycin and prednisolone solutions (100 μM each) was studied at 25°C in the absence and presence of combination drugs. Absorbance data at different time intervals was used to calculate the concentration of drug remaining. The stability of the combination was found to be more than that of the individual drugs.

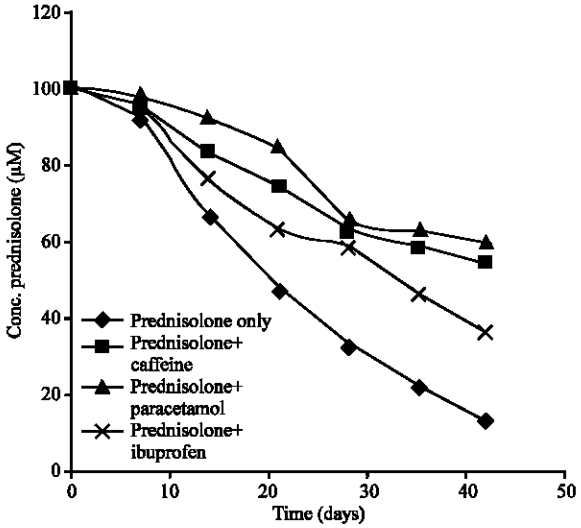

Fig. 6: Degradation of prednisolone in the absence and presence of combination drugs

It is seen that both clarithromycin and prednisolone undergo significant degradation (Fig. 5, 6). In a time period of 42 days, degradation of clarithromycin was 77% and that of prednisolone was 87%. However, the combination of these drugs with caffeine, paracetamol and ibuprofen were found to enhance the stability of both clarithromycin and prednisolone. The percentage degradation was only 64, 57 and 35% in the presence of ibuprofen, caffeine and paracetamol, respectively as compared to 77% for clarithromycin only. Similarly in the case of prednisolone, the percentage degradation was 64, 46 and 41%, respectively in the case of ibuprofen, caffeine and paracetamol as compared to 87% for prednisolone only. Again paracetamol was found to be quite effective in enhancing the stability of both the drugs.

CONCLUSIONS

The solubility as well as stability of clarithromycin and prednisolone could be enhanced by combining them with three other drugs; paracetamol/ caffeine/ ibuprofen. Solubility increase was significant only up to a certain optimum concentration of the combination drug. Paracetamol was also found to be the most effective combination drug in enhancing both the solubility and stability of clarithromycin as well as prednisolone. The magnitude of solubility enhancement was relatively smaller in the case of prednisolone as compared to clarithromycin.

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