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In vitro In vivo correlation of sustained release capsules of Metoprolol

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ABSTRACT

In vitro in vivo correlation of metoprolol tartrate sustained release capsules were studied in this investigation**.** The half-life of metoprolol is 3 to 4 hours. Peak plasma concentrations vary widely and occur about 1.5 to 2 hours after a single oral dose. In this study, non pareil seeds were prepared and coated with metoprolol tartrate using polyvinyl pyrollidone and iso propyl alcohol. Drug coated pellets were then coated with different proportion of microcrystalline wax and glyceryl di stearate using carbon tetrachloride as solvent. The release pattern of drug coated pellets and wax coated pellets were evaluated in vitro by dissolution test apparatus. Theoretical sustained release was compared with formulated sustained release. In vivo evaluation of metoprolol sustained release has been studied. A single dose was carried out in six rabbits with two sequences, cross over study. Blood samples were collected at one hour intervals. The plasma concentration of metoprolol was estimated by reverse phase HPLC. The pharmacokinetic parameters were calculated from the plasma concentration of metoprolol and time data.

The mean in vitro dissolution curve of the product is compared with the mean in vivo absorption curve generated by Wagner – Nelson method. The mean data for the in vivo percent absorbed were plotted versus time and the in vitro drug release versus time were superimposed on the first plot. The simplest way to demonstrate a correlation is to plot the percentage absorbed in vivo versus the percentage released in vitro at the same time.

INTRODUCTION:

An in vivo in vitro correlation (IVIVC) is defined as a "predictive mathematical model describing the relationship between an in vitro property of an extended release dosage forms and a relevant in vivo response, e.g. plasma drug concentration or amount of drug absorbed". The main objective of such a mathematical model is to use data collected in vitro to predict the in vivo response without having to conduct in vivo studies [1]. Three levels of IVIVC have been defined, level A describes the relationship between the entire in vitro and in vivo time profiles, whilst level B and C describe relationship between summary statistics derived from the in vitro and in vivo data. [1, 2, 3]. The level A IVIVC is considered the most informative and is consequently recommended by the food and drug administration as it can be used to predict the entire in vivo time profile [1, 3, 4].

Metoprolol tartrate is a β-adrenergic blocking agent with cardio selective activity. It is safe drug and is effective in the treatment of hypertension either alone or in combination with other anti hypertensive drug. Metoprolol is readily and completely absorbed from the gastrointestinal tract but is subject to considerable first-pass metabolism, with a bioavailability of about 50%. Peak plasma concentrations vary widely and occur about 1.5 to 2 hours after a single oral dose [5, 6]. The half-life of metoprolol is 3 to 4 hours

MATERIALS AND METHODS

Formulation of Non pareil seeds

Non pareil seeds (NPS) were prepared using 18" coating pan. Sucrose, starch, talc and heavy kaolin were used for this preparation. The developed non pareil seeds were sieved through 30/36 meshes and used as core for the preparation of drug coated pellets.

Formulation of drug coated pellets:

Non pareil seeds were coated with metoprolol (drug) using poly vinyl pyrollidone as binder. In 18" coating pan, non pareil seeds were taken and coated with

the solution of polyvinyl pyrollidone in iso propyl alcohol. The drug coated pellets were sieved through 16/22 meshes.

Formulation of Sustained Release pellets

Metoprolol coated pellets were coated with waxes for slow release of drug. Metoprolol was taken in coating pan 18" rotating at 35 RPM. Microcrystalline wax and glyceryl di stearate was dissolved in carbon tetra chloride separately and sprayed over the pellets.

In vitro Evaluation:

Dissolution test for determination of drug release was developed and validated according to International Conference on Harmonization guidelines . This studies were carried out for drug coated pellets and wax coated pellets using USP XXV apparatus (basket), rotating at 100 RPM in 0.1 N hydrochloric acid for two hours and in phosphate buffer (pH 7.4) for six hours.

In vivo Evaluation:

In vivo evaluation of the pharmacokinetic parameters were carried out in rabbits for sustained release pellets (combination of drug coated pellets and wax coated pellets). A single dose was carried out in six rabbits with two sequences, cross over study. Blood samples were collected at 0.5, 1.0, 2.0, 3.0, 4.0, 6.0, 8.0, 10 and 12 hours. The pharmacokinetic parameters were calculated from the plasma concentration of metoprolol and time data [7]. The sustained T_{max}, lower $C_{max,}$ decreased Ka and prolonged t ½ indicate a sustained release of metoprolol from sustained release pellets in comparison with immediate release dosage form.

In vitro in vivo correlation

The mean in vitro dissolution curve of the product is compared with the mean *in vivo* absorption curve generated by Wagner – Nelson method [8]. The mean data for the *in vivo* percent absorbed were plotted versus time and the *in vitro* drug releases versus time were superimposed on the first plot. However, the simplest way to demonstrate a correlation is to plot the percentage absorbed *in vivo* (obtained by Wagner Nelson method) versus the percentage released *in vitro* at the same time [9].

RESULTS AND DISCUSSION.

The prepared drug coated pellets (DC) showed 97.7% of drug released in one hour . MSR-1 was prepared by using 5 g of microcrystalline wax and 5 g of glyceryl di stearate. The drug release of 98.2% in 2 hours was observed in MSR-1.. Thus the release of Metoprolol was fast. To decrease the drug release, amount of microcrystalline wax (10 g) and glyceryl di stearate (10g) were increased. The release rate was decreased because 98.5% of drug was released by 4 hours. This showed that there was further scope in developing desired drug release. To decrease the release rate in further, 15 g of microcrystalline wax and 15 g of glyceryl di stearate were used. The results showed that 98.8% of drug was released in 6 hours. So, in next MSR-4 formulation 20 g of microcrystalline wax and 20 g of glyceryl di stearate was used. In this batch, 97.3% of drug was released in 8 hours. This slow release was achieved by increasing the thickness of the wax coating. But the 1st hour release was not complied (f2= 71.6) with theoretical sustained release. Now it was possible to combine the Drug coated pellets (without wax coating) with MSR-4 formulation (MSR-5) to get desired release rate. So 10% of drug coated pellets was blended with 90% of wax coated pellets (MSR-4). It showed the release rate is complied with theoretical sustained release (f2=97.94) and 96.72% of drug was released in 8 hours.

When Metoprolol administered as sustained release form (MSR-5), the peak blood concentration were found to be 93.2 ng/ml. Application of Wagner-Nelson method to the blood concentration data indicated slow absorption of Metoprolol from sustained release dosage form. The absorption rate constant K_a was found to be 0.526 hr^{-1} in the case of sustained release form, where as Metoprolol was administered as solution the K_a was found to decreased when Metoprolol was administered as sustained release formulation. The blood concentration of Metoprolol were stabilized and maintained within narrow range for over longer periods of time in the case of sustained release formulation, where as with Metoprolol as solution the concentration decreased rapidly. Sustained release capsule showed relative bio availability (98.47%) of when compared to Metoprolol solution.

In vitro release and in vivo absorption was correlated according to USP XXIII. A good linear relationship (r= 0.9656) was observed for the fabricated sustained release capsules MSR-5.

TABLE-I Comparison of fabricated sustained release pellets (MSR-5) with theoretical sustained release (TSR)

Time (Hrs)	pH of the medium	Cumulative Percentage Release (MSR-5)	Cumulative release in mg (MSR-5)	Theoretical sustained release (in %)	Theoretical sustained release (in mg)	f_2 value
1	1.2	34.01	42.51	35.37	44.21	97.74
2	1.2	45.69	57.11	44.61	55.76	98.58
3	7.4	55.62	69.53	53.85	67.31	96.41
4	7.4	65.51	81.89	63.05	78.81	93.88
5	7.4	72.71	90.89	72.33	90.41	99.81
6	7.4	78.74	98.43	81.57	101.96	92.47
7	7.4	88.31	104.13	90.87	113.59	93.50
8	7.4	96.72	120.9	100	125	90.75

TABLE-II Percentage of metoprolol absorbed following its oral administration as solution and in sustained release capsule formulation MSR-5

Time (hrs)	Percentage absorbed mean (± S.D)	
	Metoprolol solution IR-1	Sustained Release formulations MSR-5.
0.5	42.68±0.57	18.66±0.39
1	72.46±0.68	32.66±1.02
2	98.73±0.45	48.57±0.68
3	100	63.15±2.75
4	--	75.89±0.62
6	--	82.28±0.31
8	--	88.17±0.31
10	--	94.21±0.51
12	--	100

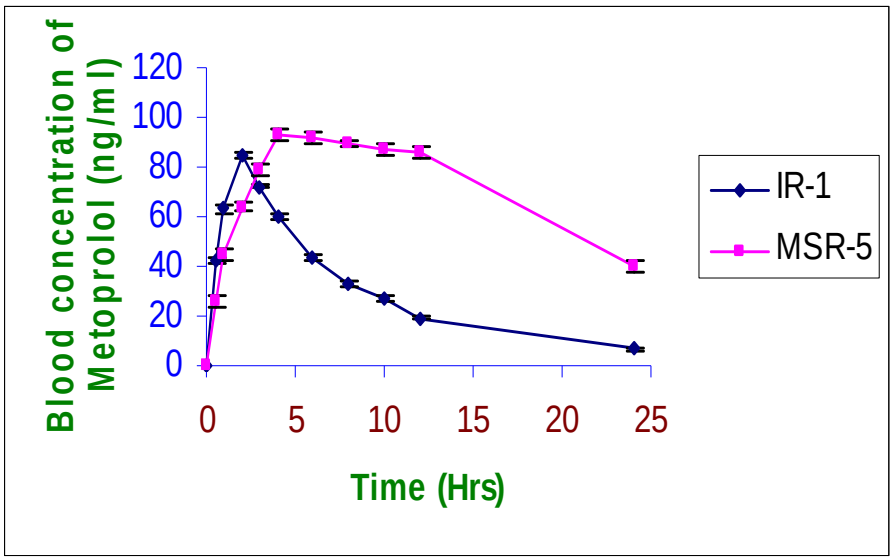

Fig. 1 Plasma concentration of metoprolol in Immediate release and sustained release

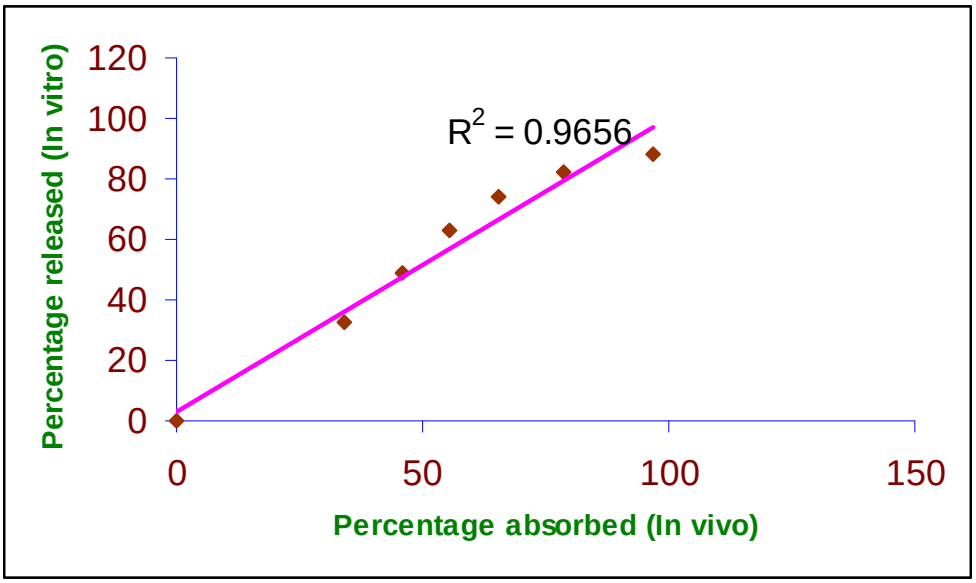

Fig. 2 In vitro in vivo correlation of metoprolol sustained release capsules

CONCLUSION

In this study, we have proved that sustained release of metoprolol sustained release capsules can be prepared by wax coating method using glyceryl di stearate and microcrystalline wax. The in vitro release characteristics of this pellets were depending upon the percentage of wax coating. The pharmacokinetics of sustained release of metoprolol were studied in fasted rabbits. The in vitro release profile is well correlated with the in vivo profile.

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