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Design, Development and Characterization of Telmisartan Controlled Release Matrix Tablets by Using Natural Polymers

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Abstract:
The purpose of present study was to develop, optimized and controlled release formulations for the oral drug delivery of Telmisartan in order to ensure maximum controlled drug release. Telmisartan controlled release matrix tablets were prepared by wet granulation method. In these preparations the natural polymers like Mangifera indica and Moringa oleifera are used to control the drug release. The pre formulation studies were performed on combination of drug with polymer by FTIR spectroscopy suggested that drug and polymers are compatible, means there is no physical and chemical interaction between drug and excipients. All the prepared formulations were evaluated for physical observation, weight variation, hardness, friability, drug content and *In vitro* drug release studies. The formulation F6 in which drug and polymers are in the ratios of 4:3 shows the 99.75 of best drug release up to 12hrs, when compared with all other formulations.

Key words: Telmisartan, mangifera indica, moringa oleifera, Controlled-release drug-delivery systems

INTRODUCTION:

The maintenance of drug content at the site of action is the primary concern with any formulation design. Some conventional dosage forms can provide poor management of plasma drug concentrations. Drug-level fluctuations due to frequent administration and variations in their absorption and/or metabolism can result in toxic effects or render the drugs ineffective. These problems can be resolved by designing new drug-delivery systems that can provide steadystate plasma concentrations of the drug(s) administered. Recently, extensive efforts have been dedicated to developing controlled-release drug-delivery systems[1]. Controlled release drug delivery systems are aimed at controlling the rate of drug delivery, sustaining the duration of therapeutic activity and/or targeting the delivery of the drug to tissue. Drug release from these systems should be at a desired rate predictable and reproducible. Among the various approaches, preparation of drug-embedded matrix tablets is one of the least complicated approaches for obtaining controlled release and is widely used in industry.[2,3]

Telmisartan is a nonpeptide angiotensin-II receptor (type AT1) antagonist. It blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin-II by selectively blocking its binding to the AT1 receptor in adrenal gland and smooth muscles of vasculature. Following oral administration, peak concentrations (C_{max}) of telmisartan are achieved in the 1st hour. The bioavailability of orally administered telmisartan is nonlinear (20–160 mg)

The aim of this research work was to design a controlled-release drug-delivery system for the angiotensin-II receptor antagonist drug telmisartan. Hypertension is one of the current prevailing diseases in the world. For this reason drug with natural polymers such as mangifera indica, moringa oleifera were used as polymers in order to improve the bioavailability by minimizing the side effects of the drug.

MATERIAL AND METHOD:

Telmisartan was gift sample from hetero drugs limited, India. Mangifera indica and Moringa oleifera was procured from Girijana Co-operative Corporation society, Tirupathi. Microcrystalline cellulose, Magnesium stearate, Talc was gift sample from S.D fine chem., Mumbai.

EVALUATION OF TABLETS

The tablets are evaluated for Appearance, Weight variation, Thickness, Diameter and Friability to meet the pharmacopeia standards.

Weight variation

20 tablets were chosen at systematic manner from each batch and were weighed accurately. Average weights of each batch were calculated. The standard deviation was calculated to determine the deviations by using the formula

Percentage deviation = (Avgwt- Individual wt/Avgwt) X100

Limit for weight variation is ±10%

Hardness

From each batch of the formulation randomly 5 tablets were selected and hardness is measured by using Monsanto Hardness Tester. Then standard deviation and average was determined, hardness was calculated.

Thickness and Diameter

10 tablets were randomly preferred from every group and measured by using Vernier calipers. The average thickness, diameter and standard deviation were calculated.

Friability

From each batch of the formulation, 20 tablets were selected and friability was determined by using Roche friabilator. A pre-weighed tablet sample was positioned in Roche type friabilator and started for 100 revolutions (25rpm). Then redust the tablets and again re-weighed. The % friability was calculated by using the formula

Friability index = (Initial wt-Final wt) x100

Limit not more than 1%

Drug content

Three tablets were chosen aimlessly from each batch and taken separately into three 100ml volumetric flasks. In each flask 10oml of Hcl buffer of pH-1.2 was poured and kept for 24hrs. After filtering the solutions, the absorbance of the filtrate was measured at 296nm. From this absorbance, drug content was determined and average and standard deviation were calculation.

Drug content = Concentration **x** Dilution factor **x** Conversion factor **x** Amount of stock solution

***In- vitro* drug release studies:**

Dissolution studies were conducted using a USP II paddle method (75 rpm, 37 °C, and 900 ml dissolution medium) with a Tablet dissolution tester .Telmisartan tablet (80mg) was exposed in a medium (pH7.5 phosphate buffer). Samples were withdrawn from the dissolution medium at predetermined intervals (10, 15, 20, 30, 45 and 60 min) and then drug concentration was determined by UV (Shimadzu) at 296nm. An equivalent amount of fresh medium was added to maintain a constant dissolution volume. The reference product and a selected batch(F6) were again taken for a dissolution study in a different media(4.5pH Phosphate buffer, 0.1N HCl, 4.5pH acetate buffer) to compare dissolution profile of a selected batch with a reference product.

Stability studies

After determining drug content, the tablets are charged for stability studies according to ICH guidelines (40±2°C and 75±55 RH) for a period of 3 months in stability chambers. The samples were taken after three months and evaluate for drug content, dissolution, related substances and physical parameters like hardness and friability.

FT-IR Spectral studies:

Drug polymer compatibility studies were performed by FT-IR (Fourier transform infrared spectroscopy). FT-IR absorption spectra of Drug, moringa oleifera, mangifera indica and Hydroxyl propyl methyl cellulose and the combination of drug and polymers were shows no significant between Drug and polymer.

Table.1 Composition of drug and polymers (in mg)

S.no	Name of the ingredients	F1(mg)	F2(mg)	F3(mg)	F4(mg)	F5(mg)	F6(mg)
1	Telmisartan	40	40	40	40	40	40
2	Mangifera indica	10	20	30	---	---	---
3	Moringa oleifera	---	---	---	10	20	30
4	MCC	195.5	185.5	175.5	195.5	185.5	175.5
5	Magnesium stearate	2	2	2	2	2	2
6	Talc	2.5	2.5	2.5	2.5	2.5	2.5
7	Total Weight(mg)	250	250	250	250	250	250

Table.2: .Physicochemical parameters of tablets

Formulation Code	Weight Variation(mg)	Thickness(mm)	Hardness(Kg/cm^3)	Friability (%)	Drug content (%)
F1	248±0.13	3.60±0.03	4.06±0.11	0.76±0.04	98.44±0.36
F2	252±0.45	3.54±0.31	4.02±0.07	0.69±0.02	99.74±0.51
F3	248±0.16	3.53±0.23	3.98±0.14	0.87±0.05	99.66±0.46
F4	251±0.21	3.52±0.08	4.00±0.16	0.74±0.01	98.56±0.65
F5	248±0.17	3.33±0.16	4.09±0.04	0.84±0.03	99.57±0.30
F6	249±0.32	3.36±0.12	4.03±0.12	0.89±0.04	98.45±0.55

Fig.1: FT-IR Spectrum of Telmisartan

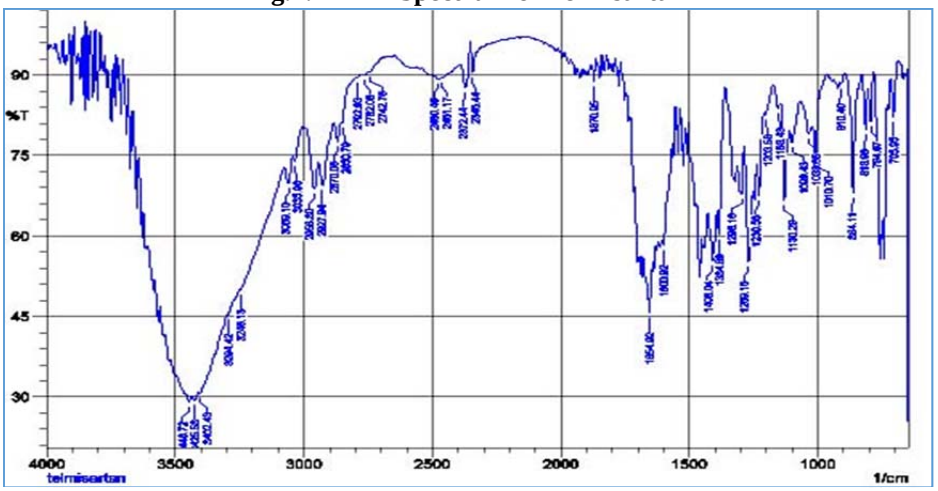


Fig 2: FT-IR Spectrum of Telmisartan with Mangifera indica

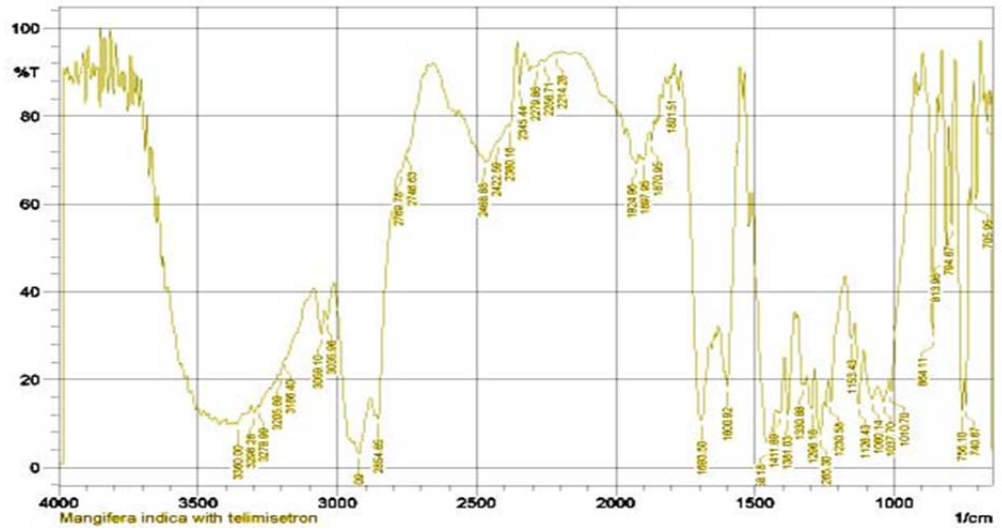


Fig.3: FT-IR Spectrum of Telmisartan with Moringa oleifera

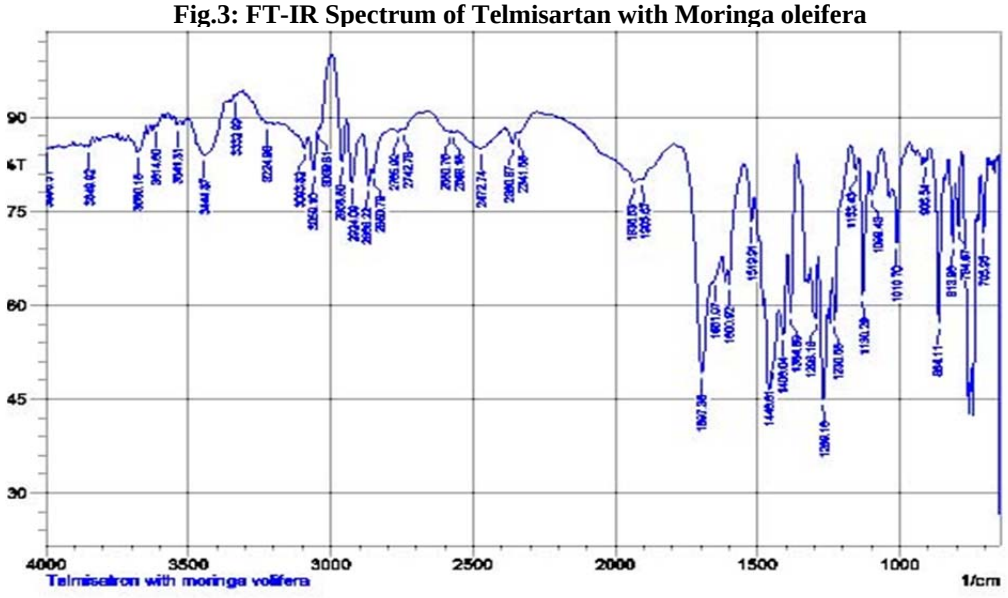
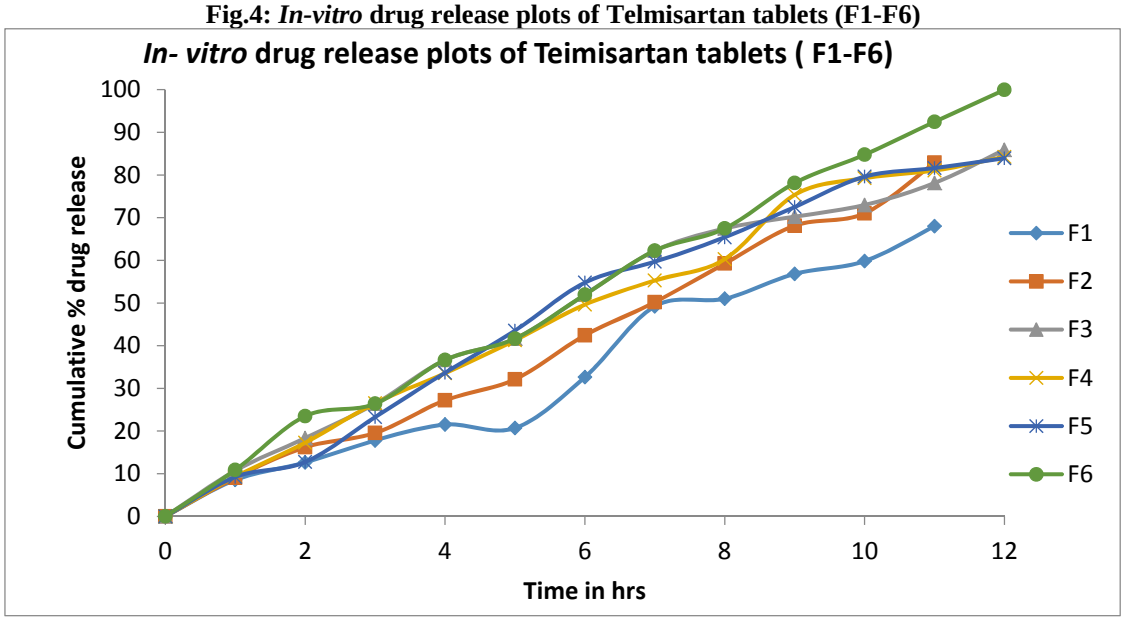


Table 3: *In-vitro* drug release data of formulation F1-F6

Time	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
1	8.55±0.17	9.05±0.15	10.7±0.19	9.3±0.16	9.25±0.18	10.9±0.16
2	12.64±0.14	16.22±0.11	18.35±0.15	17.26±0.17	12.75±0.23	23.5±0.18
3	17.8±0.15	19.56±0.18	26.4±0.16	26.52±0.19	23.26±0.22	26.4±0.23
4	21.52±0.16	27.2±0.14	36.65±0.16	33.54±0.21	33.65±0.25	36.65±0.23
5	20.7±0.12	32.12±0.12	41.65±0.21	41.26±0.23	43.53±0.11	41.65±0.11
6	32.64±0.13	42.43±0.11	51.96±0.23	49.63±0.23	54.79±0.16	51.96±0.19
7	49.23±0.13	50.19±0.14	62.26±0.16	55.28±0.14	59.67±0.19	62.26±0.17
8	51.02±0.21	59.25±0.12	67.46±0.11	60.27±0.16	65.39±0.19	67.46±0.19
9	56.83±0.23	68.12±0.18	70.23±0.24	75.34±0.19	72.5±0.15	78.12±0.24
10	59.81±0.24	71.02±0.14	72.96±0.22	79.25±0.21	79.62±0.21	84.75±0.21
11	68.01±0.19	82.9±0.14	78.12±0.16	81.05±0.22	81.62±0.25	92.45±0.25
12	----	----	85.9±0.23	84.23±0.16	83.92±0.25	99.95±0.11

Fig.4: *In-vitro* drug release plots of Telmisartan tablets (F1-F6)



RESULTS AND DISCUSSION

Matrix tablets of drug were formulated by wet granulation method by using polymers like mangifera indica, moringa oleifera and micro crystalline cellulose. The formulated matrix tablets were characterized for their physicochemical parameters like Weight variation, Thickness, Hardness, Friability, % Drug content. The results were shown in the table no 2. The FTIR spectra of Drug, mangifera indica, moringa oleifera and MCC and blend of drug and polymers were shows no interaction between drug and polymer. The FTIR spectra's are shown in the figures 1-3. The difference in the hardness of the prepared tablets ranges from 4.09±0.15 to 3.98±0.04. The thickness of the tablet was observed by using digital Vernier caliper and found to be in the range from 3.64±0.31 to 3.36±0.12. The Weight variation of the prepared tablets was bringing into within the range of 251±0.02 to 248±0.35. The strength of the prepared tablets was tested by using Roche Friabilator. The friability of all the formulations was observed within the range of 0.86±0.05 to 0.69±0.02. The drug content of all the formulations were observed within the range of99.74±0.55 to 97.44±0.36. The *In-vitro* drug release study were conducted using phosphate buffer pH 7.5 as dissolution medium and the results tabulated as and also represented graphically by taking Time12 (hrs.) on X-axis and Cumulative percentage drug release on Y-axis which was shown in figure no 4. In formulation F1 the Drug tablet were prepared with 40mg drug and 10mg mangifera indica and 195.5mg of MCC, they shown drug release of 68.01±0.19 in phosphate buffer at the end of 11 h. In formulation F2 the Drug tablet were prepared with 40mg drug and 20mg mangifera indica and 185.5mg of MCC, they shown drug release of 82.9±0.14 in phosphate buffer at the end of 11 h. In formulation F3 the Drug tablet were prepared with 40mg drug and 30mg mangifera indica and 175.5mg of MCC, they shown drug release of 85.9±0.23 in phosphate buffer at the end of 12hours. In formulation F4 the Drug tablet were prepared with 40mg drug, 10mg moringa oleifera and 195.5mgMCC, they shown drug release of 84.23±0.16in phosphate buffer at the end of 12 h. In formulation F5 the Drug tablet were prepared with 40mg drug, 20mg moringa oleifera and 185.5mg of MCC, they shown drug release of 83.92±0.25 in phosphate buffer at the end of 12 h. In formulation F6 the Drug tablet were prepared with 40mg drug, 30mg moringa oleifera and 175.5mgof MCC, they shown drug release of 99.95±0.11in phosphate buffer at the end of 12 hrs. The drug release mechanism from matrix tablets followed non-Fickian (anomalous) transport mechanism. The stability studies were conceded according to ICH guidelines for the optimized formulation i.e. F6 under accelerated stability studies (40±2ºC/ 75±5%RH). The tablets are crammed in blister packing. Then tablets were stored under 3 conditions and the tablets are withdrawn at every month and evaluate the tablet parameters like description, assay and dissolution. The tablets showed the same results as that of initial result at accelerated stability condition. It shows slight changes in drug release, but it was in acceptable limits. Study of percentage drug remaining in the best formulation reveals that there no definite changes observed to justify for drug degradation.

CONCLUSION:

It can be concluded that stable formulation could be developed by incorporating natural polymer in a definite proportion. The formulation F6 shows the 99.75 of best drug release up to 12 h, when compared with all other formulations.

CONFLICTS OF INTEREST:

All contributing authors declare no conflicts of interest.

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