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Design and development of Telmisartan transferosomes

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ABSTRACT

The aim of this research activity is to formulate Soyalecithin based transfersomal nanoparticles for percutaneous administration of Telmisartan for better management against cardiovascular diseases. The I.R peaks obtained for the physical mixture of Telmisartan was mostly identical with the pure sample of Telmisartan indicating their compatibility Telmisartan transfersomes were formulated by employing thin film hydration followed by high speed homogenization technique. Drug entrapment efficiency of optimized formulation "F3" was found to be 50.72% which was considered to be optimized based on the result. In-vitro diffusion studies of all the formulations revealed that the Telmisartan transfersomes followed first order kinetics, ascertaining Peppas mechanism. Application of Korsmeyer-Peppas equation to the data of the formulations revealed that mechanism of Telmisartan transfersomes was governed by predominant Non-Fickian diffusion (0.5>n<0.85). Based on the satisfied release studies of all the formulations, F3 was confined as the optimized formulation. The particle size of the formulation F3 was found to be 194.4nm indicating that the formulation was well within the nanosomal range. The zeta potential value of the formulation F3 was found to be -27.6mv indicating high negative surface charge which leads to its SEM analysis reports revealed that the transfersomal images were within the nanosomal range.

Based on the results, the formulation F3 was concluded as the better formulation (% Entrapment efficiency- 50.72%, Zeta Potential- 27.6mv, % Drug diffusion -58±2.4%) for the effective management of cardio vascular diseases.

1. INTRODUCTION

Telmisartan is an angiotensin II receptor antagonist used mainly for the treatment of hypertension. As with other angiotensin II receptor antagonists, Telmisartan is indicated for the treatment of hypertension. The transdermal route of drug delivery has gained great interest of pharmaceutical research, as it circumvents number of problems associated with oral route of drug administration. Recently, various strategies have been used to augment the transdermal delivery of bioactive. Mainly they include electrophoresis, iontophoresis, chemical permeation enhancers, micro needles, sonophoresis, and vesicular system like liposomes, niosomes, elastic liposomes such as ethosomes and transfersomes. Among these strategies transfersomes appear promising. A novel vesicular drug carrier system called transfersomes, which is composed of phospholipids, surfactant, and water for enhanced transdermal delivery. Transfersomes, a novel class of modified liposomes, are variously described as deformable, highly deformable, elastic or ultra-flexible liposomes or vesicles, which were first introduced in the early 1990s.

2. MATERIALS AND METHODS

Standard calibration curve graph of Telmisartan: 100 mg of Telmisartan was dissolved in 100 ml of methanol. From this 10ml of was taken and was made up to 100 ml with methanol. From this 10ml was taken and was made up to 100 ml with pH 7.4 phosphate buffer. From this stock solution (10µm/ml) series of concentrations 2, 4, 6 and 8µm/ml were prepared and the samples were scanned using UV-spectrophotometer. The λ max was found to be at 251nm. The absorbance was noted 251 nm using UV spectrophotometer.

Preformulation studies:

Characterization of Drug and Excipients: Compatibility study of Telmisartan, Soyalecithin, Span80 and Tween80 are by I.R Spectroscopy. The physicochemical compatibility between Telmisartan, soya lecithin, Span80 and Tween80 used in the research were carried out by IR Spectral studies using Perkin Elmer Fourier transform infrared spectrophotometer, Bruker, Germany, in the wavelength region between 4000cm^{-1} to 400cm^{-1}. The spectra obtained for Telmisartan, soya lecithin, and Span80 and Tween80 and the physical mixtures were compared.

Formulation of Telmisartan transfersomes: Telmisartan transfersomes were formulated by employing thin film hydration technique. For this accurately weighed quantities of Telmisartan drug, Soya lecithin, Span80 and Tween80 were dissolved in 15 ml of Solvent which is mixture of Chloroform and Methanol in the ratio of 2:1. The resultant solution was placed in 800 ml evaporating flask and subjected to rotation using rotary vacuum flask evaporator at 60 rpm maintaining at 60^0c temperature and 760mm Hg pressure until the solvent was evaporated and thin film was deposited on the walls of the evaporating flask. [Note: A chilling unit was additionally attached to the condenser for hastening the recovery of the solvent]. 20 ml of 7.4 phosphate buffer was incorporated into the flask for the hydration of the thin film under similar conditions, further size reduction with ultraprobe sonicator (vibra cell) at 80% amp and pulse at 20 on and 20 off cycles for 20 minutes with ice water bath maintained at 4ºC for uniform mixing, followed by subsequent homogenization at 15000rpm at 60ºC for 5minutes. After cooling, the transfersome dispersions were stored in glass vials covered with aluminium foils and maintained at room temperature

Determination of unentrapped drug: 10 ml of transfersomal content was placed in two centrifugal tubes separately and centrifuged with 15,000 rpm at 4^0c temperature using Remi cooling centrifuge for 1hr. The clear supernatant was decanted and the resultant precipitate was added with 5ml 7.4 Phosphate for 30 minutes under similar conditions. The suspension was decanted and the process was repeated again by adding 5ml phosphate buffer to ensure complete removal of unentrapped drug. The amount of the drug unentrapped was estimated at 251nm.

Determination of entrapped drug: For the determination of entrapped drug, 2ml of transfersomal solution was mixed with 2ml of 10% triton x-100 solution and 2ml of 7.4 Phosphate and centrifuged at 15,000 rpm, 4^0C for 30 minutes. The contents were filtered through 0.22µ membrane filter using vacuum filter. The filter was analyzed by U.V-spectrophotometer at 251 nm by suitable dilutions.

SEM analysis: One drop of diluted Telmisartan transfersomal solution was placed on a stub covered with a clean glass and subjected to SEM analysis using HITACHI S-3700 N.

Determination of average particle size and size distribution: The average particle size and size distribution of the Telmisartan transfersomal formulation was estimated using Horiba Nanopartica SZ-100. The number of particles present in the size range was considered and the average particle size was determined.

Determination of zeta potential: The zeta potential of the Telmisartan transfersomal formulation was estimated using Horbia Nanopartica SZ-100.

***In-vitro* diffusion studies:** The *in-vitro* diffusion of Telmisartan was carried out in the modified Franz diffusion cell. It consists of two chambers. The upper chamber/donor compartment holds the formulation while the lower one carries receptor or buffer medium. The dialysis membrane was placed in between the two compartments and clamped. The receptor medium is stirred by a stainless steel pin at a constant speed of 100 rpm. Physiological temperature 37±1ºC has to be maintained throughout the experiment. Aliquots (1mL each) were periodically withdrawn at suitable time intervals from the sampling port and replaced with equal volume of diffusion medium to maintain the constant receptor volume. The samples were analyzed spectrophotometrically at a wave length of 251nm for determining the concentration of the drug.

Table.1.Composition of Telmisartan Transfersomes

Formulation Code	Telmisartan (mg)	Soya Lecithin(mg)	Span80 (mg)	Tween80 (mg)	Chloroform:Methanol (2:1) (ml)
F1	20	95	5	---	15
F2	20	90	10	---	15
F3	20	85	15	---	15
F4	20	80	20	---	15
F5	20	75	25	---	15
F6	20	70	30	---	15
F7	20	95	---	5	15
F8	20	90	---	10	15
F9	20	85	---	15	15
F10	20	80	---	20	15
F11	20	75	---	25	15
F12	20	70	---	30	15

3. RESULT AND DISCUSSION

Telmisartan is an AT2 receptor blocker available for clinical use which binds to AT1 receptor with high affinity Telmisartan suppresses the maximal response to AT2 when composed with other sartans. Such action of Telmisartan is possibly due to slow dissolution kinetics of the compounds from AT1 receptor. However the major disadvantage of the drug is its shorter biological half-life. The present research is focused on the formulation of soya lecithin based nanosized transfersomes for percutaneous administration of Telmisartan in sustaining the drug release and reducing the particle size, thus leading to better therapy. Moreover it also emphasis on the minimization of the side effects with the topical administration of the drug. Telmisartan transfersomes are formulated by varying concentrations of soya lecithin and surfactants such as span80 & Tween80 surfactants as key excipients.

Compatibility studies of Telmisartan, Soyalecithin, Surfactants such as Tween80 and Span80 and their physical mixture of the excipients both individually and in combination were compared using I.R spectroscopy. The results revealed that the peaks obtained for the Telmisartan pure samples and physical mixture were found to be compatible and without changes in the functions indicating their compatibility.

Table.2.Percentage entrapment efficiency of Telmisartan Transfersomes

Formulation code	Feed drug (mg)	Unentrapped drug (mg)	%Entrapment efficiency
F1	20	4.32	47.75
F2	20	4.21	48.96
F3	20	4.05	50.72
F4	20	6.62	44.60
F5	20	6.46	42.57
F6	20	6.60	44.25
F7	20	6.75	45.65
F8	20	7.86	45.05
F9	20	4.36	47.08
F10	20	7.70	46.45
F11	20	6.79	43.96
F12	20	6.47	42.43

In-vitro diffusion studies: In-vitro diffusion studies for the release of transfersomes prepared with varying Phosphatidylcholine: surfactant molar ratios were studied. The release profiles from different transfersomal formulations were apparently biphasic release process, when a rapid release was observed during the initial phase (first 2hours) results from the release of surface adsorbed drug followed by a sustained release profile upto 24 hours.

The release from the transfersomal formulations upto 24hrs, first increased with increase inSpan80 concentration (from 5-15%w/w) in the transfersomal formulations and their decreased by further increasing in the concentration of surfactants. The high in-vitro diffusion study result was obtained for the formulation with the Tween80 as surfactant highest diffusion result was obtained for the formulation F10. In both the formulations the ratio of the Soyalecithin: Surfactant was 80:15. A possible explanation for lower drug release at low surfactant may be that the lipid membranes were more ordered and less leaky, which impeded drug release. The maximum release was observed in the concentration surfactant molecule gets associated with the phospholipid bilayer resulting in the better partitioning of the drug and resulted in the higher drug release from the vesicles. At high surfactant concentrations, the release of the drug was low due to the loss of vesicular structure and formulation of rigid mixed micelles.

Further In-vitro permeation studies of Telmisartan transfersomes revealed that the drug release from all the formulations followed first order kinetics ascertaining Peppas mechanism respectively. Application of korsmeyer -Peppas equation to the data of the formulation revealed that the mechanism of Telmisartan transfersomes is governed by predominant Non-Fickian diffusion.

A better transfersomal formulation has to possess good entrapment efficiency along with optimum release kinetics adhering to nanoparticles size range. Base on this statement F3 was considered as better formulation with entrapment efficiency (50.72 %). Identifying it was the optimized formulation. It was subjected to Particle size and Zeta potential.

The Particle size value was observed for the formulation was found to be F3 is 194.4 nm which was well within the nanosized range and possessed a zeta potential value of -27.6mv. The observed value shows a better stability and which might have attributed because of smaller particle size and higher zeta potential which indicates the most favorable factors for stability in formulations. From the polydispersity index values, it was observed that the particle sizes of various

formulations were decreased. Even though those are uniform but strictly adhered to the transfersomal range. The SEM analysis (Hitech-S-3700) transfersomal images even though distorted confined to the nanometric range, provides an additional support to the nanosized particles.

Table.3.In-vitro diffusion studies data of formulations (F1-F6)

Time (hours)	% Drug release					
	F1	F2	F3	F4	F5	F6
0	0.00	0.00	0.00	0.00	0.00	0.00
1	1.24±0.034	1.15±0.042	1.260±0.117	1.24±0.056	1.07±0.254	1.064±0.321
2	2.85±0.021	2.47±0.562	2.776±0.069	3.78±0.194	2.57±0.214	2.653±0.104
3	5.35±0.23	5.58±0.561	5.821±0.123	4.79±0.0145	5.50±0.313	5.595±0.195
4	8.25±0.074	8.24±0.013	7.106±0.214	9.21±0.042	8.33±0.106	8.250±0.423
5	12.23±0.0363	11.29±0.097	11.245±0.087	12.36±0.254	11.31±0.042	11.3±0.049
6	16.08±0.042	15.04±0.413	15.922±0.106	18.98±0.123	15.98±0.216	15.05±0.042
7	22.98±0.413	21.0±0.04	20.969±0.142	23.37±0.231	21.03±0.098	20.93±0.036
8	27.65±0.069	27.35±0.113	26.380±0.254	28.05±0.564	26.45±0.069	27.27±0.138
9	31.68±0.013	32.31±0.036	32.176±0.684	33.93±0.852	32.24±0.512	32.22±0.313
10	35.89±0.321	37.54±0.036	37.408±0.652	38.33±0.789	37.47±0.363	37.46±0.363
11	39.36±0.257	42.12±0.138	44.77±0.104	45.69±0.254	44.83±0.017	42.96±0.512
12	42.92±0.117	45.96±0.251	49.82±0.042	49.81±0.264	48.95±0.113	46.90±0.254
24	46±0.027	51±0.254	58±0.113	56±0.117	53±0.036	50±0.331

Table.4.In-vitro diffusion studies data of formulations (F7-F12)

Time (hours)	% Drug release					
	F7	F8	F9	F10	F11	F12
0	0.00	0.00	0.00	0.00	0.00	0.00
1	0.87±0.104	1.15±0.254	1.06±0.224	0.97±0.324	1.03±0.413	1.24±0.213
2	1.615±0.042	1.92±0.321	2..83±0.214	2.82±0.442	2.62±0.097	2.85±0.254
3	3.89±0.123	4.32±0.135	5.33±0.654	55.32±0.097	5.31±0.104	5.35±1.264
4	6.11±0.113	7.13±0.133	8.24±0.985	9.15±0.214	8.24±0.012	8.25±0.321
5	11.76±0.117	12.87±0.054	12.22±0.262	12.3±0.087	12.21±0.056	12.23±0.005
6	14.68±0.547	16.8±±0.253	16.06±0.321	17.07±0.512	16.04±0.066	16.08±0.214
7	21.48±0.165	21.95±0.026	22.96±0.112	23.13±0.010	22.95±0.413	22.98±0.123
8	25.14±0.458	26.53±0.984	27.63±0.230	27.81±0.125	27.63±0.042	27.65±0.216
9	28.48±0.215	29.54±0.064	31.66±0.331	33.69±0.445	31.61±0.049	31.68±0.254
10	32.08±0.254	32.64±0.214	37.72±0.215	38.09±0.225	37.70±0.113	35.89±0.010
11	35.27±0.165	35.83±0.005	40.82±0.117	41.65±0.512	40.82±0.036	39.36±0.015
12	38.562±0.258	39.11±0.251	43.96±0.384	45.02±0.331	43.95±0.138	42.92±0.331
24	41±0.365	43±0.214	47.5±0.113	48±0.524	47±0.029	46±0.032

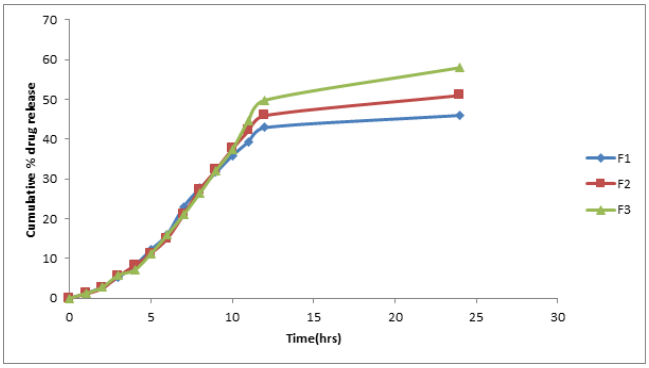

Figure.1.In-Vitro Diffusion Profile of Formulations (F1, F2, F3)

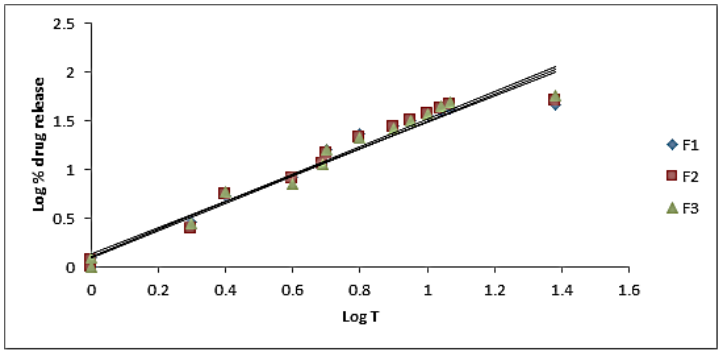

Figure.2.Peppas Plot of Formulations (F1, F2, F3)

Table.5.In-vitro drug diffusion kinetics of Telmisartan Transfersomes

Formulation code	Correlation coefficient (r^2)				Release kinetics			Exponential coefficient (n)
	Zero order	First order	Higuchi	Peppas	K (Hr^{-1})	$T_{50\%}$ (Hr)	$T_{90\%}$ (Hr)	
F1	0.8366	0.9107	0.9820	0.9845	0.0341	20.2	67.6	0.6771
F2	0.8817	0.9244	0.9649	0.9739	0.0369	18.8	62.5	0.6231
F3	0.9311	0.9421	0.9614	0.9940	0.0325	16.8	55.9	0.7268
F4	0.8482	0.9361	0.9841	0.9906	0.044	16.9	56.1	0.6231
F5	0.8621	0.9219	0.9684	0.9738	0.0386	17.9	59.6	0.6251
F6	0.7231	0.9186	0.9832	0.9836	0.0370	18.7	62.2	0.6451
F7	0.9181	0.9067	0.9561	0.9842	0.0299	23.2	77.1	0.7167
F8	0.7478	0.9139	0.9834	0.9846	0.0310	22.3	74.2	0.6468
F9	0.8318	0.9126	0.9761	0.9823	0.0350	19.8	65.1	0.7218
F10	0.7761	0.9099	0.9764	0.9836	0.0362	19.1	63.5	0.6594
F1I	0.8611	0.9102	0.9857	0.9931	0.0352	19.7	65.4	0.8026
F12	0.8106	0.9107	0.9879	0.9888	0.0341	20.3	67.5	0.5761

4. CONCLUSION

Based on the above observation formulation "F3" was considered as the optimized formulation. (% Entrapment efficiency- 50.72%, Zeta Potential-27.6mv, % Drug diffusion -58±2.4%) for the effective management of cardio vascular diseases. It was observed that the drug entrapment efficiency was found to be decreased and varying the concentrations with the optimized formulations.

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