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Formulation Design and Evaluation of Telmisartan Mucoadhesive Microspheres

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ABSTRACT

The main aim of the present work was to formulate and characterize oral sustained release mucoadhesive microspheres of Telmisartan. Telmisartan is an angiotensin II receptor antagonist (angiotensin II receptor blocker, ARB) used in the management of hypertension and has low aqueous solubility and bioavailability. This drug also undergoes first-pass metabolism. To overcome all these problems telmisartan mucoadhesive microspheres were developed to control the release rate of the drug and target to the specific site of the body to make an enormous impact in the formulation and development of novel drug delivery system and also improve efficient absorption and enhances oral bioavailability of the drug due to high surface to volume ratio. It also provides intimate contact of the drug delivery system to the absorbing mucous membrane for sustaining the drug action. This is a new oral drug delivery system that was developed and utilized both the concepts of sustained release and mucoadhesiveness to obtain a unique drug delivery system that could remain in the intestine and control the drug release for a longer period.

INTRODUCTION:

Controlled drug delivery:

Nowadays, very few drugs are coming out of research and development and already existing drugs are suffering the problem of resistance due to their irrational use specifically in the case of drugs like antibiotics. Hence, change in the operation is a suitable and optimized way to make some drugs more effective by a slight alteration in drug delivery. In contrast to drug delivery systems, the word novel is searching for something out of necessity. The drug has to be delivered for a prolonged period and many medicines have to be taken simultaneously in case of chronic patients. [1, 2]

Frequent administration of a drug is necessary when those have a shorter half-life and all these leads to a decrease in patient's compliance. To overcome the above problems, various types of controlled release dosage forms are formulated and altered, so that patient compliance increase through prolonged effect, the adverse effect decreases by lowering peak plasma concentration. [2]

The controlled release dosage form maintaining a relatively constant drug level in the plasma by releasing the drug at a predetermined rate for an extended period. There are significant challenges in developing controlled release formulations for drugs with poor aqueous solubility which requires both solubilization and engineering of release profile. [1, 3]

The desire to maintain a near-constant or uniform blood level of a drug often translates into better patient compliance as well as the enhanced clinical efficacy of the drug for its intended use. Numerous SR oral dosage forms such as membrane controlled system, matrices with water-soluble/insoluble polymers or waxes, and osmotic systems have been developed; intense research has recently focused on the designation of SR systems for poorly water-soluble drugs. [3]

Telmisartan is an angiotensin II receptor antagonist (angiotensin II receptor blocker, ARB) used in the management of hypertension. It is practically insoluble in water. A new oral drug delivery system was developed utilized both the concepts of sustained release and mucoadhesiveness to obtain a unique drug delivery system that could remain in the intestine and control the drug release for a longer period.[3,4]

MATERIALS AND METHODS:

MATERIALS:

Telmisartan was obtained as a gift sample from A.S. Joshi & Company, Mumbai. HPMC K4M, HPMC K100M, Na CMC, Carbopol 974 P obtained from S. D. Fine Chem. Ltd., Mumbai. Carbopol 974 P, Chitosan obtained from Loba Chemie Pvt. Ltd., Mumbai.

METHOD:

Preparation of mucoadhesive microsphere by Ionic gelation technique:

The iontropically-gelled microspheres containing Telmisartan were prepared using calcium chloride ($CaCl_2$) as a cross-linker. Aqueous dispersions of sodium alginate were prepared separately using distilled water by heating at 60ºC using a magnetic stirrer. On the other hand, polymer aqueous dispersions were prepared separately using distilled water at room temperature using a magnetic stirrer. Both the dispersions were well mixed together with stirring for 10 min at 1000 rpm using a magnetic stirrer to prepare sodium alginate dispersion mixtures containing 500 mg of different selected polymer concentrations in all formulations. Afterward, the required quantity of the drug was added to the dispersion mixture maintaining the ratio of drug to polymer 1:1 in all formulations. The final polymer-blend dispersion mixture of alginate-polymer containing drug was homogenized for 20 min at 1000 rpm using a homogenizer and ultrasonicated for 5 min for de-bubbling. The resulting dispersion was then added via a 14-gauge needle. The added droplets were retained in the $CaCl_2$ solution for 15 min to complete the curing reaction and to form rigid microspheres. The wet microspheres were collected by decantation and washed two times with distilled water and dried at 40ºC for 24 h. The prepared dried microspheres containing the drug were stored in a desiccator until used. [5, 6]

Drug Excipient Compatibility Study:

Fourier Transform Infrared Spectroscopy Study:

FTIR spectroscopy was used to determine the functional group present in the pure drug sample. The FTIR spectrum of pure Telmisartan was showed the characteristic peaks at 740 cm^{-1}, 1128 cm^{-1}, 1268 cm^{-1}, 3057 cm^{-1}, 1695 cm^{-1} & 862 cm^{-1} were due to aromatic C-H stretching, C-N stretching, C=N stretching, aromatic C-H stretching, C=O

stretching and O-H stretching respectively. IR spectra of Telmisartan is as follows:[13,14]

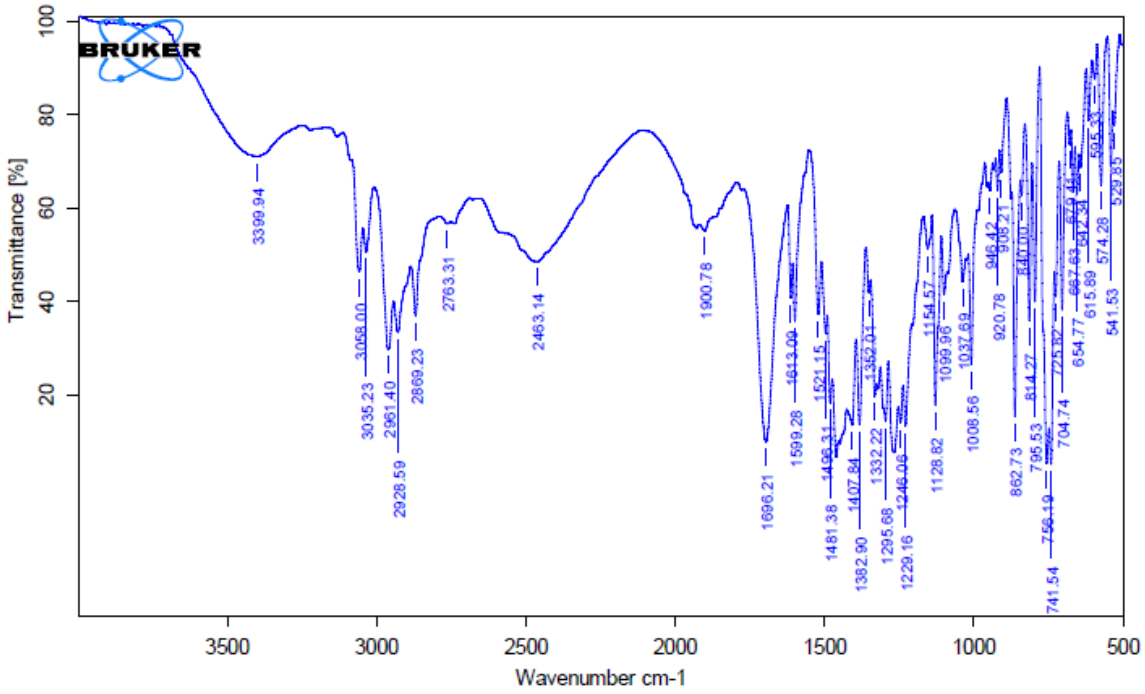

Figure No. 1: IR Spectra of Telmisartan

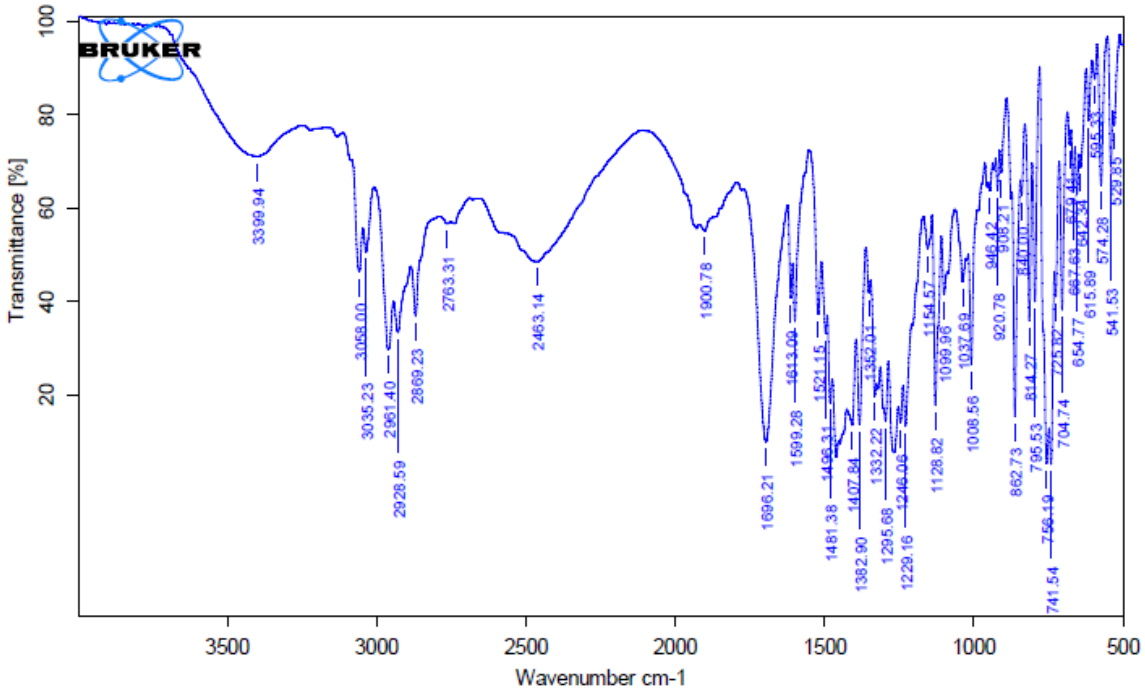

Figure No. 2: IR Spectra for the Mixture of Drug + Carbapol 974 P

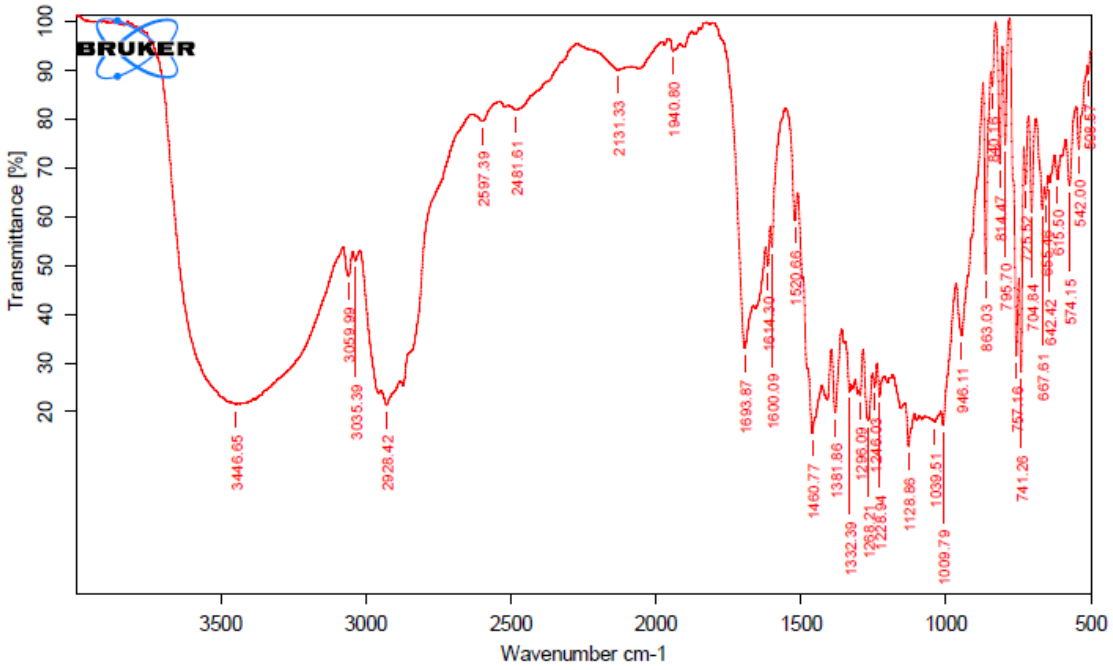

Figure No. 3: IR Spectra for the Mixture of Drug + HPMC K 4 M + HPMC K 100 M

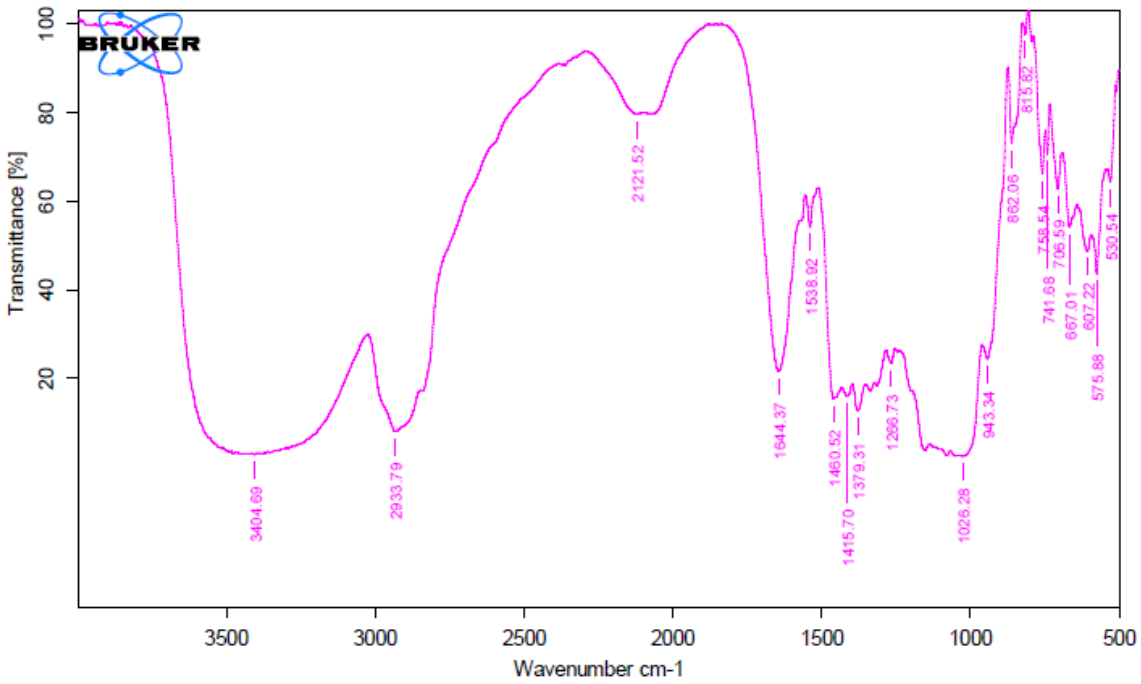

Figure No. 4: IR Spectra for the Mixture of Drug + Sodium Alginate + Sodium CMC

The samples of pure drug and formulas were dispersed in KBr powder and compressed into pellets at a pressure of 6000 Kg/cm^2. Spectral measurements were obtained by powder diffuse reflectance on the FT-infrared spectrophotometer.

Inference: The FTIR spectra for the pure drug and formulations were shown in Fig 1 - 4. The spectra of drug and polymers employed were showed a broad peak at the same place as the peak observed at the spectrum of the pure drug has been observed, which indicated that there was no chemical interaction with the polymers.

FORMULATION OF TELMISARTAN MUCOADHESIVE MICROSPHERES BY IONIC GELATION TECHNIQUE [Drug: sodium alginate: mucoadhesive polymers 1:4:1]

Table No. 1: Formulation Design of Telmisartan mucoadhesive microspheres

Ingredients	F1	F2	F3	F4	F5	F6
Telmisartan(mg)	500	500	500	500	500	500
Sodium Alginate(mg)	2000	2000	2000	2000	2000	2000
Carbopol 974 P(mg)	-	500	-	-	-	-
HPMC K4M(mg)	-	-	500	-	-	-
HPMC K 100M(mg)	-	-	-	500	-	-
Na CMC(mg)	-	-	-		500	-
Chitosan(mg)	-	-	-	-	-	500
Calcium chloride(gm)	10	10	10	10	10	10
Distilled water(ml)	QS	QS	QS	QS	QS	QS

Characterization of prepared microspheres:

1. Percentage yield:

The production yields of microspheres prepared by the ionic gelation technique were found to be 35.65 to 49.35 as shown in table 2. [7]

Table No. 2: Percentage yields of the microspheres (Preliminary formulation)

Formulation code	% yield
F1	35.65±0.02
F2	49.35±0.03
F3	45.51±0.04
F4	48.45±0.05
F5	46.36±0.05
F6	42.87±0.01

*Each reading is an average of three determinations (Mean ± S.D) (n=3).

2. Drug content & Entrapment efficiency :

The drug content and drug entrapment efficiency of all formulation have been summarized in Table 3 & 4 Drug content range from 56.87 to 94.86 and drug entrapment efficiency from 51.39 to 45.95 respectively. [8, 9, 10]

Table No. 3: Drug content of the microspheres (Preliminary formulation)

Formulation code	Theoretical drug content (mg)	Practical drug content (mg)
F1	100	56.87±0.01
F2	100	61.93±0.02
F3	100	71.26±0.03
F4	100	69.43±0.04
F5	100	80.23±0.05
F6	100	94.86±0.06

Table No. 4: Entrapment efficiency (%) of the microspheres

Formulation code	Entrapment efficiency (%)
F1	58.28±0.02
F2	69.73±0.03
F3	51.39±0.04
F4	56.14±0.01
F5	66.49±0.02
F6	59.87±0.03

*Each reading is an average of three determinations (Mean ± S.D) (n=3).

3. Loose surface crystal study:

The loose surface crystal studies lend a hand to estimate the excess amount of drugs attached to the surface of microspheres after a successful drug entrapment. This study was executed with all the formulations and the results are depicted in Table 5. It was found in the range of 36.08 to 46.95 for formulation F1 to F6 which is the attribute to the initial burst of expelled medication from the sphere surface.[10,11]

Table No. 5: Loose surface crystal study of the microspheres

Formulation code	Loose surface crystal study (%)*
F1	46.95±0.03
F2	45.20±0.03
F3	39.99±0.02
F4	42.95±0.04
F5	38.73±0.02
F6	36.08±0.01

*Each reading is an average of three determinations (Mean ± S.D) (n=3).

4. Size distribution of microspheres:

The size distributions in terms of the average diameter of the microspheres were determined by an optical microscope method. A compound microscope fitted with a calibrated ocular micrometer and a stage micrometer was used to count at least 50 microspheres. The mean of the particles was taken into account. The microspheres were uniform in size in each formulation and the mean size ranged from 243.5±0.01to 1008.5±0.02 which was in the arbitrary particle size range of 10-1000µm. The particle size ranges are shown in Table 6.

Table No. 6: Particle size analyses of the microspheres

Formulation code	Particle size (µm)*
F1	670±0.03
F2	243.5±0.01
F3	432.4±0.02
F4	540±0.04
F5	642.5±0.03
F6	1008.5±0.02

*Each reading is an average of three determinations (Mean ± S.D) (n=3).

5. Micromeritics properties of the prepared microspheres:

The flow properties of microspheres such as the angle of repose, Carr's Index, and Hausner's ratio are represented in Table 7.

a. Angle of repose: The angle of repose of all the formulations showed excellent flowability and ranged from 16.52 to 22.20.

b. Carr's index: The carr's index of all formulations exhibited excellent flow properties and ranged from 8.42 to 13.65.

c. Hausner's ratio: Hausner's ratio of all the formulated microspheres exhibited good flow properties which ranged from 1.01 to 1.3.

Table No. 7: Micromeritics properties of the microspheres

Formulation code	Angle of repose (°)	Carr's index	Hausner's ratio
F1	17.20	11.45	1.1
F2	16.52	12.23	1.02
F3	21.30	8.42	1.04
F4	17.25	13.65	1.02
F5	19.12	11.26	1.01
F6	22.20	10.12	1.3

6. Percentage moisture loss:

This study was carried out for a period of 24 h. The percentage of moisture loss was found to be in the range of 5.26 to 11.23 for the formulation F1 to F6 as summarized in Table 8. Percentage moisture loss increases concerning time. [12, 14]

Table No. 8: Percentage of moisture losses of the microspheres

Formulation code	% Moisture loss*						
	1 hr	**2 hr**	**3hr**	**4hr**	**5hr**	**6hr**	**24 hr**
F1	5.10	5.26	5.26	5.26	5.26	5.26	5.26
F2	4.10	5.26	5.26	5.26	5.26	5.26	5.26
F3	0	0	0	0	0	0	0
F4	5.26	5.26	5.26	5.26	5.26	5.26	5.26
F5	0	0	0	0	0	0	0
F6	4.32	09.12	10.02	12.32	11.06	12.02	11.23

*Each reading is an average of three determinations (Mean ± S.D) (n=3).

7. Swelling Index:

The results reveal that all the formulations swelled rapidly when immersed in phosphate buffer pH 6.8. It is reported that adhesive properties and cohesiveness of mucoadhesive

polymers are generally affected by their swelling behavior. From the calculated data it is seen that, the after swelling index for formulations as F4>F3>F5>F2>F6>F1. After 24hrs HPMCK4M higher swelling was observed for formulation F4 (90%) containing mucoadhesive polymer as compared to other mucoadhesive polymer-based formulations. [13, 15]

Table No. 9: swelling index of the microspheres (100mg microspheres)

Formulation code	% Swelling Index*						
	1 h	2 h	3 h	4 h	6 h	18 h	24 h
F1	35	40	45	47	50	62	73
F2	50	53	55	61	63	70	80
F3	51	53	55	57	61	76	88
F4	55	57	59	61	65	70	90
F5	32	35	44	48	53	44	82
F6	52	55	59	61	62	64	76

*Each reading is an average of three determinations (Mean ± S.D.) (n=3).

Figure No. 5: Schematic pictures for swelling of microspheres

8. *In- vitro* wash-off test:

The adhesion time of microspheres followed the rank order F4 > F5> F3 > F2> F6 > F1. Results indicated that the viscosity of the polymer was strongly associated with the

adhesion. Viscosity was directly proportional to the mucoadhesive property. The microspheres consisting of sodium alginate in combination with various mucoadhesive polymers exhibited good mucoadhesive properties as observed in the in-vitro wash-off test. [15, 16]

Table No. 10: *In-vitro* wash-off test of the mucoadhesive microsphere in phosphate buffer pH 6.8

Formulation	% Microspheres adhering to tissue at various time intervals						
	0.5 h	1 h	2 h	3h	4h	5h	6h
F1	80	78	69	62	39	17	-
F2	84	78	83	69	48	23	20
F3	85	89	84	72	49	26	22
F4	96	90	87	78	55	39	30
F5	87	81	76	73	44	30	24
F6	80	70	65	60	48	21	18

*Each reading is an average of three determinations (Mean ± S.D.) (n=3)

9. *In-vitro* drug release study:

The *in-vitro* drug release studies of Telmisartan were initially carried out in phosphate buffer pH 6.8 for 22 hrs. Sodium alginate-based microspheres not significantly retarded the drug released at the examined time points throughout up to 24 h.

The release of Telmisartan was mainly driven by the permeation of the drug through the hydrophobic polymer membrane. All these formulations show an initial burst effect which was due to the presence of drug particles on the surface of the microspheres as also inferred from loose surface crystal study.

Sodium alginate is widely regarded as a sustained-release matrix because of its properties of water-insoluble and low permeability. Its effect on drug release could be influenced by various grades of HPMC, Na CMC, carbopal, and chitosan as a polymer, which forms hydrophilic passages inside the microspheres which helps the drug to diffuse out easily as compared to other mucoadhesive polymers.

From the in vitro dissolution data & plotted it is seen that after 24 hr study, formulation F4 (HPMCK100M) showed better drug release retardation as compared based formulation shows less to other formulations. In the case of HPMCK100M is might be 94% it's swelling as well as excellent mucoadhesion properties. The viscosity of the mucoadhesive polymer has the main role in both bioadhesion and sustained action. [17, 18]

Table No. 11: Cumulative % drug releases of different Formulations (F0-F6)

Time (hr)	Formulation Code						
	Pure drug (F0)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0	0
0.5	50.73	38.15	30.50	4.16	3.21	4.23	20.91
1	52.32	41.14	35.82	8.53	5.91	6.71	21.44
2	55.32	45.16	42.46	14.68	6.44	15.44	39.56
4	69.58	51.23	56.16	53.15	25.86	51.51	55.62
6	88.51	69.54	70.16	69.14	38.19	62.36	63.51
8	99.46	78.96	79.56	78.56	44.26	78.53	78.72
10	-	99.12	82.51	83.16	48.56	82.36	89.56
12	-	-	98.16	91.42	54.98	91.59	99.46
14	-	-	-	96.59	71.53	99.81	-
16	-	-	-	99.46	82.12	-	-
18	-	-	-	-	88.15	-	-
22	-	-	-	-	94.38	-	-
24	-	-	-		99.51	-	-

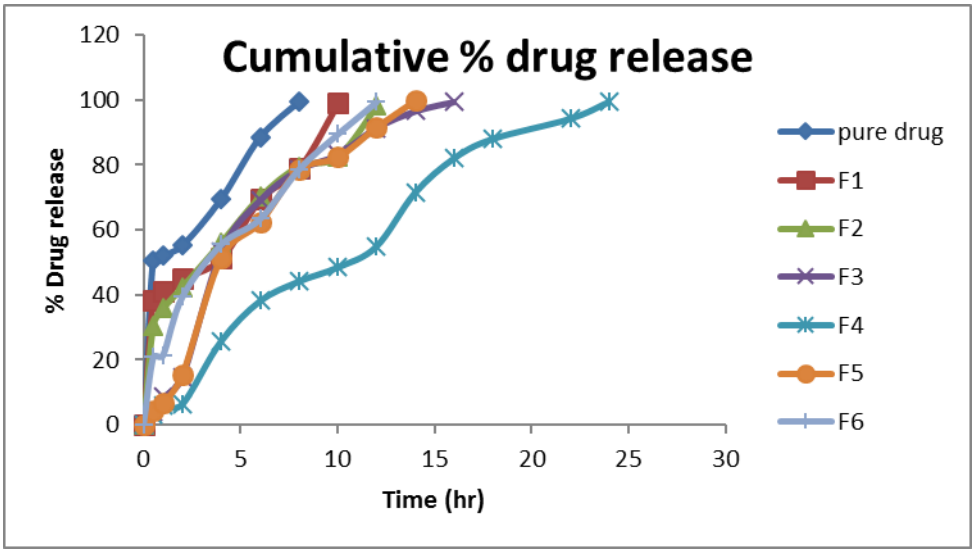

Figure No. 6: Cumulative % drug releases of different Formulations (F1-F6)

10. Scanning Electron Microscope (SEM) Study:

The shape and surface morphology of optimized chitosan-based mucoadhesive microspheres were observed by SEM study (Joel Scanning Microscope JSM-5800, Japan). The SEM analysis was carried out using an accelerating voltage of 20 kV after they were gold-sputtered (Jeol Jee 4B SVG-IN, Peabody, USA). The result is shown in Figure:

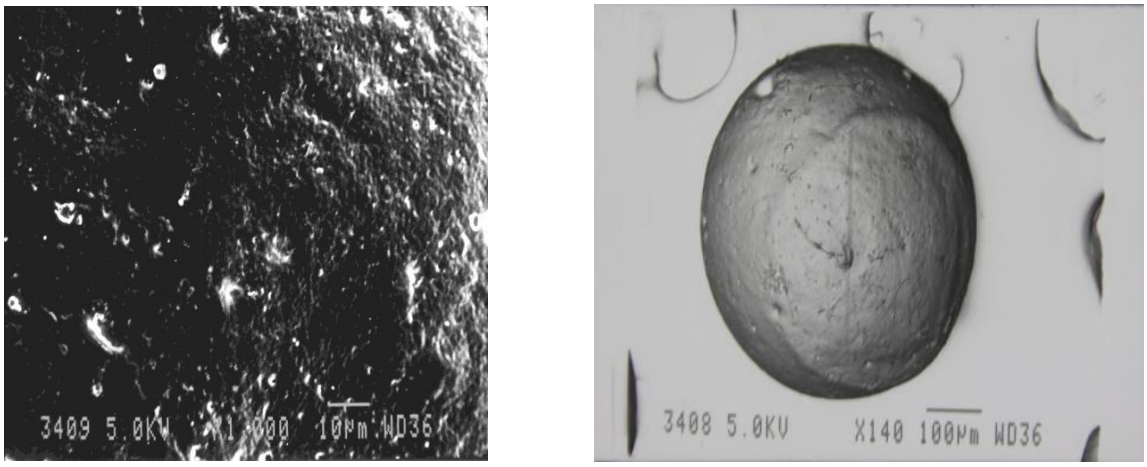

Figure No. 7: Scanning Electron Microscopy of optimized formulation at low resolution (a) and high resolution (b)

CONCLUSION:

Telmisartan loaded mucoadhesive microspheres were successfully prepared by the ionic gelation method. After evaluating all the parameters formulation F4 (HPMCK100M) showed better drug release retardation as compared based formulation shows less to other formulations. The drug release in the case of HPMCK100M is 99.51% at 24hrs because of its swelling as well as excellent mucoadhesion properties. From the above research findings, it was conducted that Telmisartan is a suitable drug candidate to formulate a mucoadhesive drug delivery system (microspheres) for better treatment of hypertension by reducing the frequency of drug optimization than another delivery system.

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