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Research Article

MUCOADHESIVE MICROBEADS OF METFORMIN HCL: A PROMISING SUSTAINED DRUG DELIVERY SYSTEM

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ABSTRACT
The present work was investigated to reduce the dosing frequency, improve patient compliance, to improve gastric residence and to decrease GI side effects by designing and evaluating controlled Release Mucoadhesive (CRM) microbeads of Metformin hydrochloride for effective control of diabetes type-II. Microbeads were prepared by employing ionic gelation method by using various natural and synthetic polymers such as sodium alginate as main polymer and sodium carboxy methyl cellulose(SCMC), carboxy methyl cellulose(CMC), methyl cellulose (MC), poly vinyl pyrrolidine (PVP) as co-polymers which mainly containing mucoadhesive property. These polymers are used with various proportions using calcium chloride as across linking agent. The mucoadhesive property of four polymers is in the following order (SCMC > CMC > MC > PVP).Twenty formulations were prepared. The mucoadhesive beads were characterized for micromeritic properties such as bulk density, tapped density, hausner's ratio, compressibility index, angle of repose, percentage drug content, entrapement effieciency, swelling index, *In-vitro* drug release, mucoadhesion test, drug kinetics and FT-IR studies. The drug entrapment efficiency increased progressively with increasing concentration of co - polymer resulting in the formation of larger microbeads entrapping greater amounts of the drug. No significant drug-polymer interactions were observed in FT-IR studies. The kinetics of drug release and their mucoadhesive nature in vitro using goat intestinal mucosa was also investigated at physiological pH 1.2 HcL. The effective mucoadhesion property with controlled release profile was observed from optimized mucoadhesive beads consisting of Sodium alginate and SCMC (1:5). The prepared microspheres exhibited prolonged drug release as the concentration of co-polymer increased, as the SCMC polymer concentration increases the mucoadhesion increased and the drug release rate decreased at higher concentration of sodium alginate.
KEY WORDS: Metformin hydrochloride, Mucoadhesion, Diffusion, Viscosity.

INTRODUCTION

The concept of the advanced drug delivery systems especially those offering a sustained and controlled action of drug to desired area of effect, attained great appeal for nearly half a century. Sustained release or prolonged release dosage forms are designed to achieve prolonged therapeutic effect by continuously releasing the drug over an extended period of time after administration of single dose. Since the frequency of drug administration is reduced, patient compliance can be improved and the frequency of drug administration can be made more convenient as well. The blood level oscillation characteristic of multiple dosing of conventional dosage form is reduced.

Further, the process of targeting and site specific delivery with absolute accuracy can be achieved by attaching bioactive molecule to liposome's, bio- erodible polymer, implants, monoclonal antibodies and various particulate carriers (E.g., nanoparticles and microspheres / microbeads, etc.). The micro particulate delivery systems are considered and accepted as a reliable means to deliver the drug to the target site with specificity, if modified, and to maintain the desired concentration at the site of interest without untoward effects. Mucoadhesive systems permit a given drug delivery system to be incorporated with bio / mucoadhesive agents, enabling the device to adhere to the stomach (or other GI) walls, thus resisting gastric emptying. A bio / mucoadhesive substance is a natural or synthetic polymer. The characteristics of these polymers are molecular flexibility, hydrophilic functional groups, and specific molecular weight, chain length, and conformation. Furthermore, they must be nontoxic and non - absorbable.

Mucoadhesive drug delivery systems interact with the mucus layer covering the mucosal epithelial surface, and mucin molecules and increase the residence time of the dosage form at the site of absorption. The drugs which have local action or those which have maximum absorption in gastrointestinal tract (GIT) require increased duration of stay in GIT. Thus, mucoadhesive dosage forms are advantageous in increasing the drug plasma concentrations and also therapeutic activity. Mucoadhesive drug delivery systems facilitate an intimate contact of the dosage form with the underlying absorption surface and thus improve the therapeutic performance of the drug. In recent years, many such mucoadhesive drug delivery systems have been developed for oral, buccal, nasal, rectal and vaginal routes for both systemic and local effects[1].

Metformin Hydrochloride (MH) is an oral hypoglycaemic agent belongs to biguanides class.[2] MH has been reported to control glucose level and improve lipid profile in type-II diabetics.It has a short half-life (1.5- 4.5 hours), so repeated administration (250mg twice or thrice daily) is required to maintain effective plasma concentrations. It is absorbed from upper intestine within 6 hours. Administrations of a sustained- release, once a day Metformin hydrochloride dosage form could reduce the dosing frequency and improve the patient compliance[3]. Thus, in the present study, MH is selected as a model drug and SCMC, CMC, MC and PVP are chosen as a mucoadhesive polymer for design and evaluation sustained release microbeads. This study was performed to investigate the mucoadhesion and sustaining effect of co-polymers (SCMC, CMC, MC, PVP) on metformin hydrochloride release from the sodium alginate beads adhered on the fresh goat stomach mucosa was studied.

MATERIALS AND METHODS

Metformin Hcl and Sodium carboxy methyl cellulose (SCMC) was a gift sample from Glukem pharmaceuticals Pvt.Ltd (Hyderabad, India). Sodium alginate, methyl cellulose (MC) and poly vinyl pyrollidone was obtained from Loba chemie Pvt. Ltd (Mumbai, India). Calcium chloride obtained from Thermo fisher scientific Pvt. Ltd (Mumbai,

India). Carboxy methyl cellulose (CMC) obtained from Merck specialities Pvt. Ltd (Mumbai, India).

Method of preparation of mucoadhesive microbeads of metformin HCL

Mucoadhesive microbeads of metformin HCL is prepared by ionotropic gelation technique by using different proportions of sodium alginate and co - polymer (MC, CMC, SCMC, PVP) ratio as indicated in Table -1. Initially weigh the required amount of sodium alginate and co-polymer dissolved in 100ml of water to get a uniform dispersion[4, 5]. To the above dispersion add 200mg of the drug and mix it well. Then obtained dispersion containing sodium alginate: co-polymer and drug is filled in the syringe with needle size of 24 in to 10% w/v $cacl_2$ solution drop by drop to get spherical micro beads. The added droplets were retained in the calcium chloride solution for 20 minutes to complete the curing reaction and to produce spherical rigid micro beads. The micro beads were collected and dried over night at room temperature. The obtained micro beads were stored in desiccators for further evaluation tests.

***In – vitro* characterization of prepared microbeads**

Assay of metformin HCL

A standard solution of metformin hydrochloride was prepared by dissolving 100 mg of the drug in 100 ml of distilled water and further diluted with water to get primary stock solution (1000 µg / ml). From the primary stock pipette out 1ml and make up to 100ml with water to get secondary stock solution (10 µg/ml). From this secondary stock solution pipette out 1ml and make up to 100ml with water to get final stock solution. From this final stock take1ml ,2ml, 3ml, 4ml, 5ml, 6ml, 7ml, 8ml, 9ml,10ml in to ten volumetric flasks (100m.l capacity) for serial dilution. Finally make up with water upto mark.

Micromeritic properties:

Angle of repose (θ)

The angle of repose of prepared micro beads was determined by glass funnel method, weigh required quantity of 2gm of the prepared using following equation[6].

$$\theta = \tan^{-1} h / r$$

Where,

θ = angle of repose

h = height of the pile and

r = radius of the powder cone

Bulk density

Bulk density of formulated micro beads was determined by taking a known mass of 2gm of formulated micro beads in a 5 ml graduated measuring cylinder which is attached to the bulk density apparatus. The bulk density was calculated by following equation[6].

Bulk density = Weight of micro beads in gram / Bulk volume of micro beads in cm^3

Tapped density

Tapped density of micro beads was determined by tapping method using measuring cylinder containing weighed amount of 2gm of formulated micro beads. The cylinder was dropped three times from a height of one inch at an interval of two seconds. Tapped density of microspheres was calculated by following equation[6].

Tapped density = Mass of micro beads / Volume of micro beads after tapping

Carr's compressibility index

This is an important property in maintaining uniform weight. It is calculated using following[6]

% Compressibility Index = Tapped density – Bulk density X 100 / Tapped density

Hausner's ratio

Hausner's ratio can be calculated by formula[6]

Hausner's Ratio = Tapped Density X 100 / Bulk Density

Particle size and its distribution

The particle size for the prepared micro beads can be measured by optical microscope. The size distribution analysis was done by sieving technique using standard sieves (16, 18, 20 and 25) according to monograph. Weighed quantity of 2gm of the formulated micro beads were placed on the coarsest sieve on the top and allow it for shaking for 5min using mechanical gyratory shaker. The amounts retained on different sieves were weighed. The mean particle size of the microbeads was calculated by the formula[7].

Mean Particle Size = Σ (Mean Particle Size of the Fraction X Weight Fraction) / **(**Weight Fraction)

Swelling study

The swelling index of the formulated beads was carried out in 10ml water and simulated bio- fluids (pH 1.2 and pH 7.4). Drug loaded beads were equilibrated in different test tubes at 37ºC for 12hrs hours. The test tubes were withdrawn at different intervals; the beads were filtered and transferred into a small beaker and then weigh. Swelling index can be calculated by the formula[8].

Swelling index = $W_t - W_0 \times 100 / W_0$

Where,

W_t = weight of micro beads observed at 8^{th} hr

W_0 = the initial weight of micro beads

Percentage drug content and encapsulation efficiency

100 mg of accurately weighed formulated micro beads were dissolved in 100ml distilled water until get dissolved completely. Filter the solution and take 0.5 ml of aliquot and make the suitable dilution to get 5µg / ml and analyzed for the drug content at 233nm wavelength against blank. Percentage drug content was calculated by [7]

Drug Content (mg) = (Absorbance × Slope ± Intercept) × Dilution factor / 1000

It gives drug content for 100 mg of micro beads from that calculate drug content for total quantity of micro beads , from actual drug content, the value of encapsulation efficiency was determined using the formula given below.

Encapsulation efficiency = Actual drug content x 100 / Theoretical drug content

***In – vitro* Drug Release Studies**

The release rate of drug from the prepared micro beads was determined using United States Pharmacopeia (USP) Dissolution testing apparatus I (basket method). The dissolution test was performed using 900 ml of pH 1.2 HCL buffer for 8hrs. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus hourly and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45µ membrane filter and diluted to a suitable concentration with of pH 1.2 HCL buffer. Absorbance of these solutions was measured at 233nm using a UV/Visible spectrophotometer.

Mucoadhesion testing by *in- vitro* wash- off method

The goat stomach mucosa was used for in – vitro mucoadhesion evaluation. The mucosa was removed and cut in to pieces 2cm long and 2cm wide and were rinsed with 2ml of 0.1N Hcl (pH 1.2). 100microbeads of each were scattered uniformly on the surface of the stomach mucosa. After 20 minutes, the tissue was taken out and fixed on a polyethylene support at an angle 45^0. About 100 micro beads were spread on to each wet rinsed tissue specimen and immediately thereafter the support was hung on to the arm of a USP tablet disintegrating test machineas shown in Figure-1.

When the disintegrating test machine was operated, the tissue specimen was given a slow, regular up- and down movement in the test fluid at 37^0C contained in a 1L vessel of the machine. At one end of 30minutes, at the end of 1hr, and at hourly intervals up to 8hrs the machine was stopped and the number of micro beads still adhering to the tissue was counted[9].

Fourier Transform- Infrared Spectroscopic Analysis (FT-IR)

Drug polymer interactions were studied by FT-IR spectroscopy. One to 2mg of pure drug, placebo microbeads, and drug loaded microbeads samples were weighed and mixed properly with potassium bromide to a uniform mixture. A small quantity of the powder was compressed into a thin semitransparent pellet by applying pressure. The IR-spectrum of the pellet from 450- 4000cm^{-1} was recorded taking air as the reference and compared to study any interference[10].

RESULTS AND DISCUSSION

All the micromeritic properties for the prepared twenty formulations were performed, that are bulk density, tapped density, hausner's ratio, compressibility index and angle of repose as per the I.P and these properties for all the prepared twenty formulations as shown in Table - 2 were within the limits. Particle size and its size distribution were done by optical microscopy and sieve analysis method. Results revealed that the particle size was more for the M_5 formulation as indicated in Table-3 compared to other prepared formulation this was because of the fact that by increasing the polymer concentration results in enhanced the viscosity of the preparation which leads to increase in the emulsion drop size and finally results in increase the particle size of the microbeads as shown in Figure- 2. Swelling index data for all the prepared formulations were done and M_5 formulation shows the maximum swelling index of 85% for 8 hrs in pH 1.2HCL. Swelling index was increased with increase in the co-polymer concentration (Table – 4). Results showed that the swelling index for sodium carboxy methyl cellulose formulations was high due to high gelling character when compared to other formulations containing co-polymers as represented in Figure -3. Results also concluded that poly vinyl pyrrolidone had the low swelling index due to its low capacity to form the gel. Drug content and encapsulation efficiency were calculated for all the prepared formulations (Table-5). Results showed that formulation M_5 exhibit more encapasulation efficiency and M_{16} exhibits lesser encapsulation efficiency compared to all other prepared formulations. Increase in the co-polymer concentration leads to increase in the percentage drug content. And the results showed that the percentage drug content and encapsulation efficiency for sodium carboxy methyl cellulose containing formulations was high due to high gelling property when compared to other formulations containing co- polymers were as poly vinyl pyrrolidone containing formulations had the low percentage Drug content and encapsulation efficiency(Figure - 4, 5). The drug release profiles of the drug from the prepared formulations were shown in Table-6 and figure – 6 (a, b), 7, 8 and 9. the mucoadhesive microbeads prepared with SCMC (sodium carboxy methyl cellulose) as co-polymer has good drug release profile of 79% for 7hrs (M_5) when compared to other formulations containing varying proportions of sodium alginate as a main polymer and co- polymers. This was due to the fact that by increasing the density of polymer matrix at high concentration results in an increase in diffusional path length.This may finally decrease the drug release from polymer matrix. Finally it was concluded that all the hydrophyllic co- polymers which were used for the study provides the sustained release mucoadhesive microbeads of metformin HcL as per the limits according to the USP. The mucoadhesive property for sodium carboxy methyl cellulose was high as indicated in Table – 7 and shown in Figure- 10 due to high swelling index and the mucoadhesive property for poly vinyl pyrrolidine was low. It was concluded that the mucoadhesive property increases by increasing the copolymer concentration. From the data of drug release, it was found that, all the mucoadhesive microbead formulations follow diffusion mechanism for the drug release. The Higuchi square root equation describes the release from systems where the solid drug is incorporated in the beads and the rate of drug release is related to the rate of drug diffusion. FT-IR spectra of Metformin HCL , Sodium alginate : PVP , Sodium alginate : SCMC, Sodium alginate : CMC, Sodium alginate : MC (1:1) & prepared formulations were recorded. The Metformin HCL present in the formulations M_1, M_6, M_{11},M_{16} was confirmed by FT- IR (Figure 11-19). No predominant drug interaction was detected .The region 3600-3200cm^{-1} was a stretching region of the functional group (N-H), 2820-2780 cm^{-1} (N-CH_3), 1680- 1620 cm^{-1} (C=C), 1652-1550 cm^{-1} (C=NH), 1190-1130 cm^{-1}(C≡N). All These Peaks were appeared in pure metformin HCL and all prepared formulations indicating no drug interactions between drug and excipients. All the spectra which were obtained from the polymer and the co- polymer were studied and it was found that there was no interaction between main polymer and co- polymers.

CONCLUSION

The study was undertaken with the aim to formulate and evaluate the sustained release mucoadhesive microbeads of Metformin Hcl using sodium alginate as polymer and SCMC, CMC, MC, PVP as co- polymers. The microbeads have been utilized to obtain prolonged and uniform release in the stomach for development of a once daily formulation. In the present study, preparation of metformin hydrochloride microbeads, evaluation of Drug Delivery System (DDS) in vitro, prediction of the release, and drug release pattern to match target release profile was investigated. Microbeads were prepared by Ionotropic gelation method using SCMC,CMC, MC and PVP as the rate controlling polymer and 200 mg of metformin hydrochloride per batch and it's *in-vitro* performance was evaluated by the usual pharmacopoeia and other tests such as, Drug polymer compatibility (FT-IR scan),Yield (%), Particle size analysis, Drug entrapment efficiency, *In - vitro* release studies. Where the polymer ratio increases, the particle size may also increases, thus entrapment efficiency increases, hence the release profile was extended. The adhesion of microbeads to the stomach mucosa of goat was evaluated as the mean percent of microbeads remain adhered after defined period of washing. Results indicating that the polymer to drug ratio had a significant effect on mucoadhesive property. From the above study it has been noticed that as the concentration of copolymer (SCMC, CMC, MC and PVP) associated with the main polymer increases, mucoadhesive property increases and when the concentration of the main polymer (sodium alginate) increases, the mucoadhesive property of the microbeads decreases. The developed Microbeads of metformin hydrochloride may be used in clinical for prolonged drug release in stomach for at least 8 hrs, thereby improving the bioavailability and patient compliance.

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Table 1: Development of Different Formulations Containing, Varying Proportions of Polymer

Formulation code	Drug (mg)	$CaCl_2$ (%w/ v)	Sodium alginate (gm)	Sodium Carboxy methyl cellulose (SCMC) (gm)	Carboxy Methyl cellulose (CMC) (gm)	Methyl cellulose (MC) (gm)	Poly vinyl pyrollidone (PVP) (gm)
M_1	200	10	1	1	-	-	-
M_2	200	10	3	1	-	-	-
M_3	200	10	5	1	-	-	-
M_4	200	10	1	3	-	-	-
M_5	200	10	1	5	-	-	-
M_6	200	10	1	-	1	-	-
M_7	200	10	3	-	1	-	-
M_8	200	10	5	-	1	-	-
M_9	200	10	1	-	3	-	-
M_{10}	200	10	1	-	5	-	-
M_{11}	200	10	1	-	-	1	
M_{12}	200	10	3	-	-	1	-
M_{13}	200	10	5	-	-	1	-
M_{14}	200	10	1	-	-	3	-
M_{15}	200	10	1	-	-	5	-
M_{16}	200	10	1	-	-	-	1
M_{17}	200	10	3	-	-	-	1
M_{18}	200	10	5	-	-	-	1
M_{19}	200	10	1	-	-	-	3
M_{20}	200	10	1	-	-	-	5

Table 2: Micromeritic Properties of Various Prepared Formulations

Formulation code	Bulk density (gm / cc)	Tapped density (gm / cc)	Hausner's ratio	Compressibility index (%)	Angle of repose (θ)
M_1	0.40 ± 0.01	0.44 ± 0.01	110 ± 1.52	19 ± 0.52	19.13 ±0.15
M_2	1.0 ± 0.10	1.0 ± 0.10	100 ± 1.52	24. 2 ± 0.50	24.22 ±0.30
M_3	0.57 ± 0.10	0.66 ± 0.01	115.7 ± 0.26	13.6 ± 1.0	22.78 ±0.35
M_4	0.66 ± 0.01	0.66 ± 0.01	100 ± 1.0	20 ± 1.05	21.80 ±0.49
M_5	0.66 ± 0.01	0.8±0.10	121.2 ± 0.64	17.5 ± 1.00	26.56 ±0.45
M_6	0.5 ± 0.10	0.6 ± 0.10	132 ± 1.0	24.4 ± 1.0	10.08±0.05
M_7	0.8 ± 0.10	1.0 ± 0.15	125 ± 1.0	20 ± 1.0	12.40 ±0.26
M_8	0.66 ± 0.01	0.66 ± 0.1	100 ± 1.0	13.6 ± 0.50	19.79 ±0.45
M_9	0.30 ± 0.01	0.36 ± 0.01	120 ± 1.0	16.6 ± 0.57	21.80 ±0.47
M_{10}	0.23 ± 0.01	0.26±0.01	113.0 ± 0.45	11.53 ± 1.0	21.80 ±0.47
M_{11}	0.5 ± 0.07	0.5 ± 0.10	100 ± 1.0	20 ± 1.0	09.46±0.01
M_{12}	0.66 ± 0.07	1.00 ± 0.10	151.5 ± 0.75	34 ±1.0	11.39 ±0.15
M_{13}	0.5 ± 0.10	0.66 ± 0.10	132 ± 1.52	24.4 ± 0.088	12.407 ±0.1
M_{14}	0.5± 0.10	0.66 ± 0.01	132 ± 1.0	24.4 ± 1.01	19.76 ±0.32
M_{15}	0.5 ± 0.10	0.5 ± 0.17	100 ± 1.0	24.4 ± 1.0	30.96 ±0.40
M_{16}	0.66 ± 0.01	0.66±0.01	100 ± 1.52	21.2 ± 1.1	16.69 ±0.20
M_{17}	0.66 ± 0.01	1.0±0.01	100 ± 1.52	34 ± 1.52	19.79 ±0.2
M_{18}	0.8 ± 0.015	1.0±0.10	125 ±1.0	20 ± 0.56	15.10 ±0.1
M_{19}	0.33 ± 0.01	0.33 ± 0.15	100 ± 1.52	24.2 ± 0.43	20.30 ±0.25
M_{20}	0.25 ± 0.01	0.33 ± 0.01	132 ± 1.52	24.2 ± 0.43	23.74 ±0.36

Table 3: Particle Size and Size Distribution of Various Prepared Formulations

Formulation code	Particle size (µm)	Size distribution (µm)
M_1	1150±2.0	1161.70 ±0.36
M_2	1310±2.60	1172.7 ±0.36
M_3	1370±1.52	1178.6 5 ±0.32
M_4	1510±2.08	1179.10 ±0.26
M_5	1530±1.52	1180 ±0.15
M_6	1170±1.52	1158.92 ±0.45
M_7	1190±1.52	1161.47 ±0.15
M_8	1220±2.64	1177.30 ±0.15
M_9	1260±1.0	1180 ±0.15
M_{10}	1280±2.51	1180 ±0.25
M_{11}	710± 1.52	929.75 ± 0.36
M_{12}	880±1.0	1149.72 ±0.36
M_{13}	970±2.08	1180 ±1.0
M_{14}	1160±2.51	1180 ±1.0
M_{15}	1320±2.51	1250.4 ±0.30
M_{16}	720±2.0	781.32 ±0.15
M_{17}	850±0.57	1086.55 ±0.4
M_{18}	1320±1.52	1175.65 ±0.3
M_{19}	1360±2.08	1180 ±0.1
M_{20}	1430±1.0	1180 ±0.26

Table 4: Swelling Study of Various Prepared Formulation

Formulation code	Swelling index (using pH 1.2HcL) in time intervals (hr)							
	1st hr	2nd hr	3rd hr	4th hr	5th hr	6th hr	7th hr	8th hr
M_1	51	54	56	59	63	71	74	79
M_2	46	48	51	56	59	63	69	74
M_3	49	50	53	58	60	68	70	76
M_4	54	56	59	61	67	75	79	81
M_5	56	61	67	69	73	77	82	85
M_6	50	53	55	58	61	69	71	77
M_7	45	46	49	51	57	60	66	71
M_8	47	49	51	56	58	64	67	74
M_9	53	54	57	60	66	74	78	80
M_{10}	55	60	65	68	71	75	80	83
M_{11}	49	81	53	56	60	67	70	75
M_{12}	43	45	47	49	56	60	65	69
M_{13}	45	46	49	54	56	61	66	71
M_{14}	51	53	55	59	64	73	77	79
M_{15}	53	58	63	67	70	73	79	81
M_{16}	35	46	51	54	58	66	69	71
M_{17}	31	42	47	48	51	58	61	67
M_{18}	29	39	44	46	51	56	63	69
M_{19}	46	51	54	57	61	69	74	76
M_{20}	49	53	59	61	67	70	73	77

Table 5: **Percentage Drug content and Encapsulation Efficiency of Various Prepared Micro Bead Formulation**

Formulation code	% Drug content	% Encapsulation efficiency
M_1	0.68±0.05	69.12±0.37
M_2	1.37±0.01	77.56±0.50
M_3	1.54±0.01	78.76±0.41
M_4	1.37±0.08	87.59±0.55
M_5	2.40±0.05	90.09±0.58
M_6	1.20±0.06	47.20±0.30
M_7	2.40±0.06	58.69±0.25
M_8	1.02±0.05	63.52±0.40
M_9	0.68 ± 0.5	71.59±0.30
M_{10}	2.40 ± 0.1	86.41±0.70
M_{11}	0.51±0.02	51.89±0.58
M_{12}	0.85±0.04	68.80±0.30
M_{13}	1.02±0.02	73.71±0.51
M_{14}	1.37±0.05	77.15±0.81
M_{15}	1.37±0.05	86.07±0.46
M_{16}	0.68±0.11	37.13±0.88
M_{17}	0.85±0.03	43.67±0.05
M_{18}	0.85±0.05	56.19±0.58
M_{19}	1.20±0.18	74.47±0.20
M_{20}	2.05±0.03	79.27±0.32

Table 6(a): **Cumulative Percentage Drug Release of Various Prepared Micro Bead Formulations (M_1 - M_{10})**

Time (min)	Formulation code and its Cumulative % drug release									
	M_1	M_2	M_3	M_4	M_5	M_6	M_7	M_8	M_9	M_{10}
15	5.445	5.14	4.95	5.54	5.84	5.39	5.049	4.99	5.54	5.59
30	10.99	10.72	9.99	11.23	12.19	10.33	10.14	10.04	11.11	12.15
45	15.62	16.11	15.78	15.97	19.13	16.29	15.11	15.19	16.92	19.17
60	20.45	21.51	23.30	22.81	26.92	22.90	20.36	20.24	22.51	26.17
120	26.23	28.45	28.51	28.59	34.98	28.44	25.55	25.44	28.50	33.49
180	32.11	29.305	33.96	34.63	43.70	34.26	31.75	30.69	34.52	40.97
240	42.16	33.84	39.90	47.67	51.34	40.47	36.39	36.03	40.56	48.93
300	51.44	39.43	45.15	57.56	67.40	46.72	41.79	41.43	46.50	55.13
360	61.24	45.11	51.17	60.90	70.52	60.97	56.19	54.79	61.75	64.15
420	69.88	61.21	57.71	71.10	79.55	70.77	70.58	68.25	70.95	72.51

Table 6(b): **Cumulative Percentage Drug Release of Various Prepared Micro Bead Formulations (M_{11} – M_{20})**

Time (min)	Formulation code and its Cumulative % drug release									
	M_{11}	M_{12}	M_{13}	M_{14}	M_{15}	M_{16}	M_{17}	M_{18}	M_{19}	M_{20}
15	4.900	4.851	4.75	4.95	5.49	4.85	4.75	4.65	4.95	5.44
30	9.85	9.75	9.60	10.04	11.03	9.85	9.60	9.40	9.94	10.93
45	14.99	14.80	14.75	15.19	18.90	14.89	14.55	14.25	15.04	18.31
60	20.19	19.89	19.70	21.13	25.98	19.99	19.55	19.20	20.19	25.74
120	25.39	25.04	24.79	27.17	33.11	25.14	24.60	24.25	25.39	33.01
180	30.73	30.24	29.94	33.25	40.34	30.39	29.7	29.35	30.64	40.34
240	36.67	35.49	35.24	39.39	48.00	35.73	37.84	34.50	35.89	47.71
300	42.66	40.78	40.59	45.58	51.82	41.13	40.04	39.66	41.28	48.16
360	58.01	56.18	55.93	60.43	61.82	55.98	54.74	54.30	56.23	58.01
420	68.90	67.02	66.67	70.33	71.87	68.70	65.98	65.43	71.23	71.62

Table 7: Mucoadhesive Test Data for Various Prepared Formulations

Formulation code	Mucoadhesive test in time (min) for 100 beads							
	60	**120**	**180**	**240**	**300**	**360**	**420**	**480**
M_1	80	72	63	55	43	32	30	29
M_2	92	81	77	72	69	66	64	63
M_3	94	90	87	84	82	77	74	72
M_4	95	92	90	87	85	83	80	79
M_5	97	95	93	90	85	84	80	80
M_6	75	71	69	54	42	30	29	26
M_7	90	83	74	62	55	52	50	49
M_8	92	82	73	72	66	62	60	55
M_9	94	86	73	70	65	63	61	57
M_{10}	95	88	82	79	75	73	70	68
M_{11}	88	82	77	72	65	48	36	27
M_{12}	90	81	75	66	61	56	49	43
M_{13}	93	88	85	81	74	72	65	52
M_{14}	92	84	81	78	76	65	61	53
M_{15}	93	92	81	78	72	69	67	64
M_{16}	75	60	55	41	37	35	28	22
M_{17}	80	87	73	68	65	53	42	35
M_{18}	83	80	75	71	63	59	55	52
M_{19}	91	87	82	80	76	71	68	50
M_{20}	90	84	80	77	74	73	60	61

Figure 1: Mucoadhesive Test for Prepared Formulation

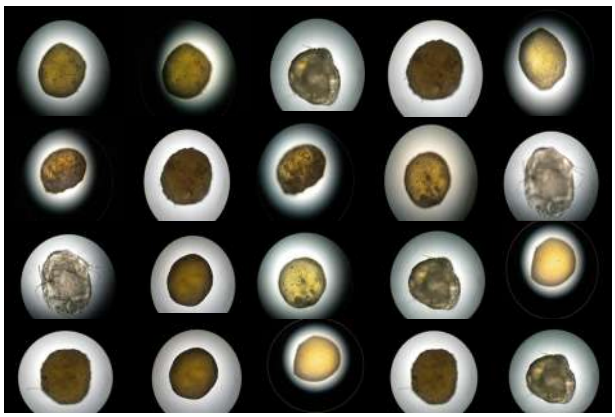


Figure 2: Optical Microscopic View of Various Prepared Formulations

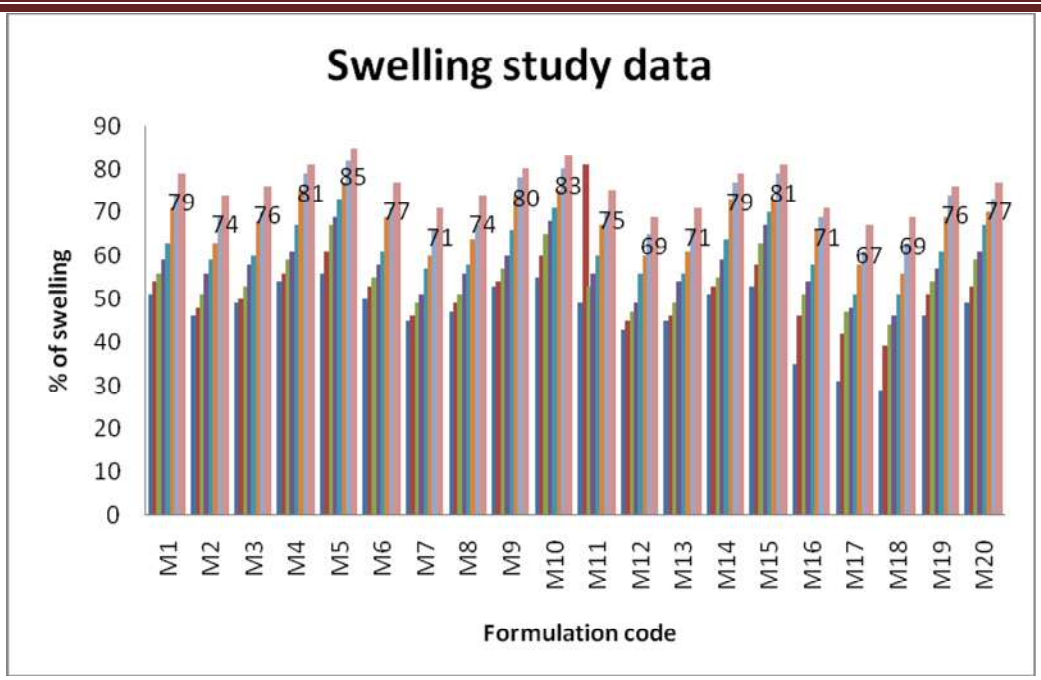


Figure 3: Swelling Study Data of Various Prepared Formulations

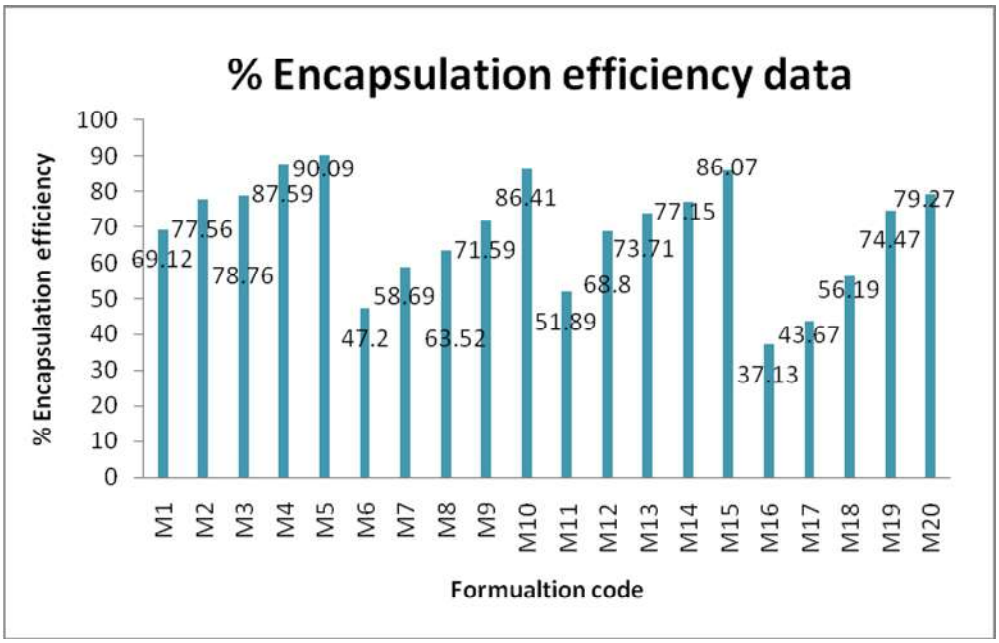


Figure 4: Encapsulation Efficiency Data of Various Prepared Formulations

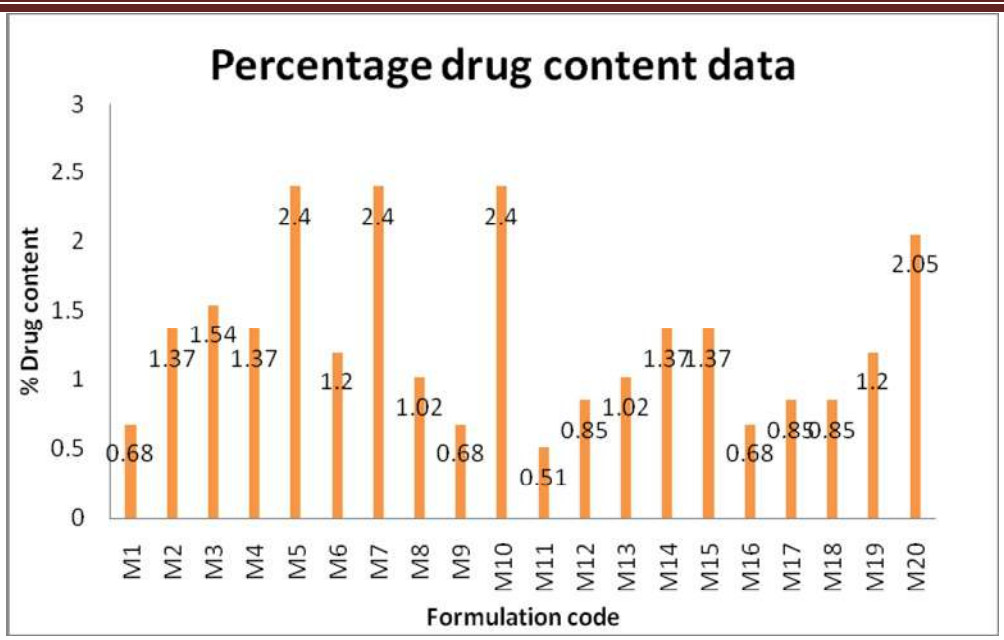


Figure 5: Drug Content data of Various Prepared Formulations

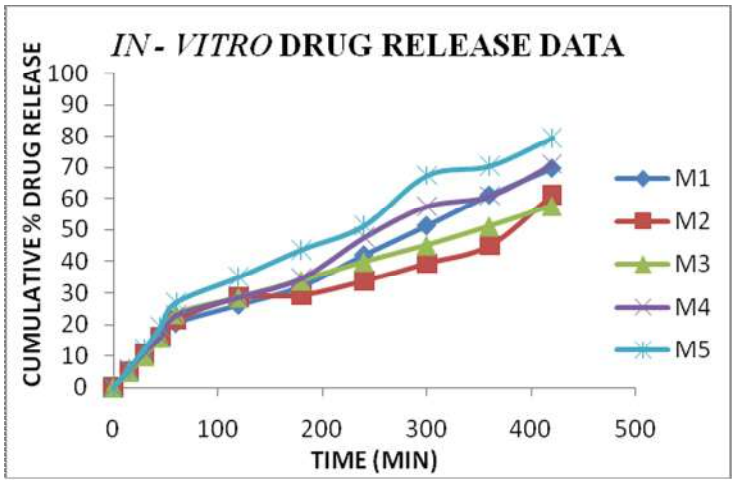


Figure 6: Percentage Drug Release of Formulations Containing Sodium Alginate: Sodium Carboxy Methyl Cellulose at Various Time Intervals

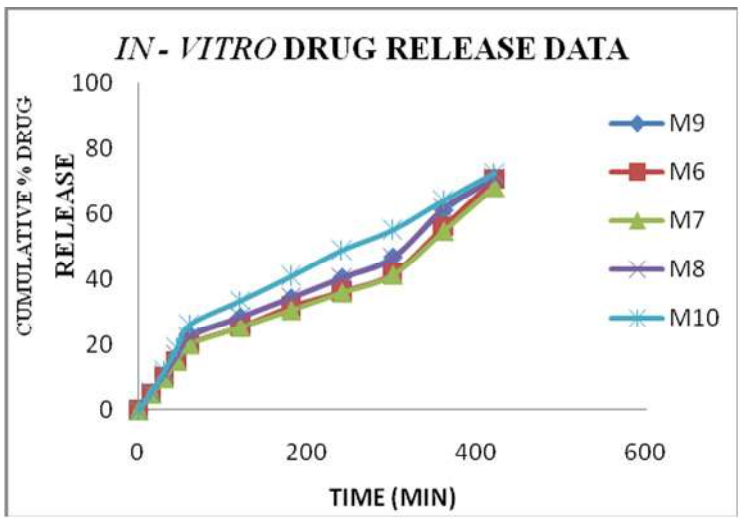


Figure 7: Percentage Drug Release of Formulations Containing Sodium Alginate: Carboxy Methyl Cellulose at Various Time Intervals

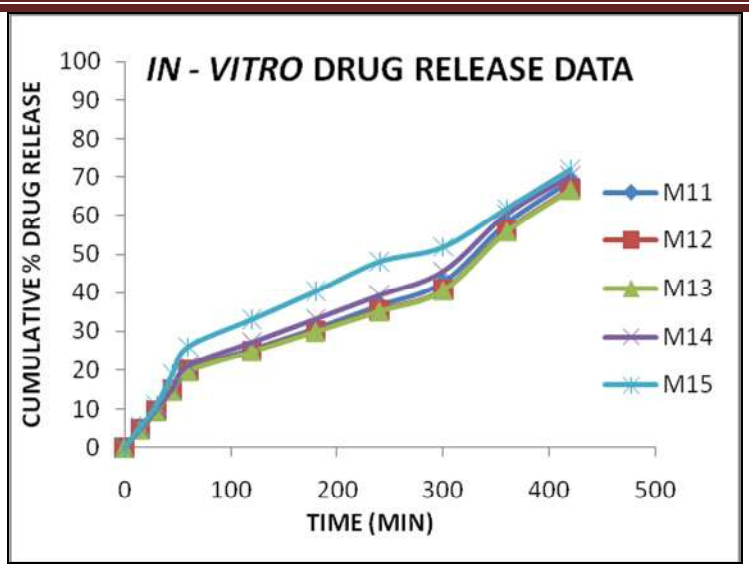


Figure 8: Percentage Drug Release of Formulations Containing Sodium Alginate: Methyl Cellulose at Various Time Intervals

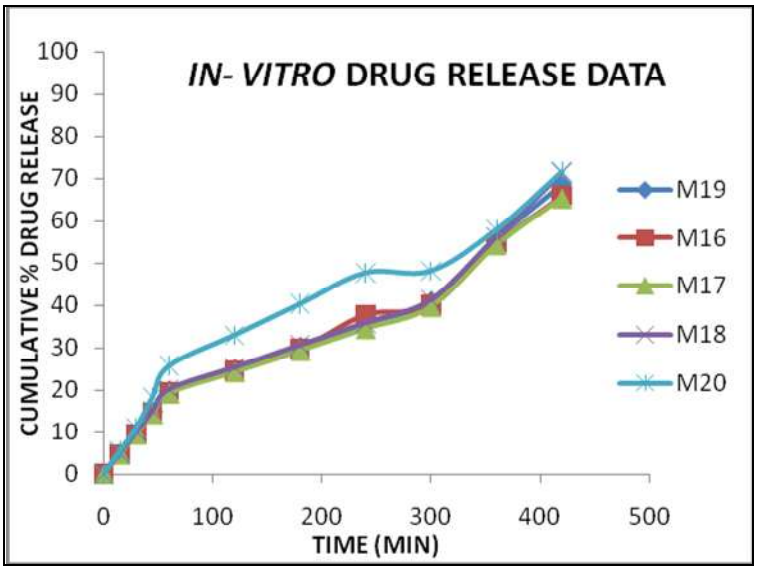


Figure 9: Percentage Drug Release of Formulations Containing Sodium Alginate: Poly Vinyl Pyrrolidone at Various Time Intervals

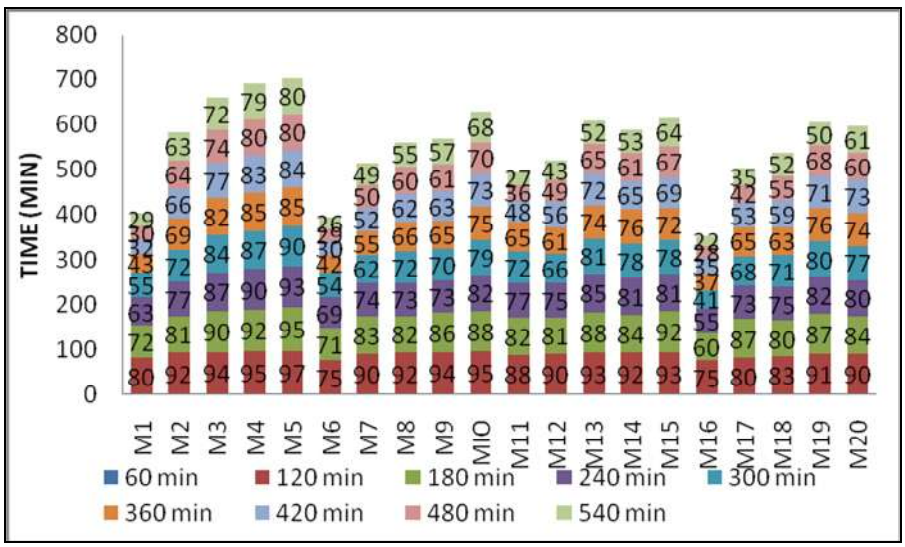
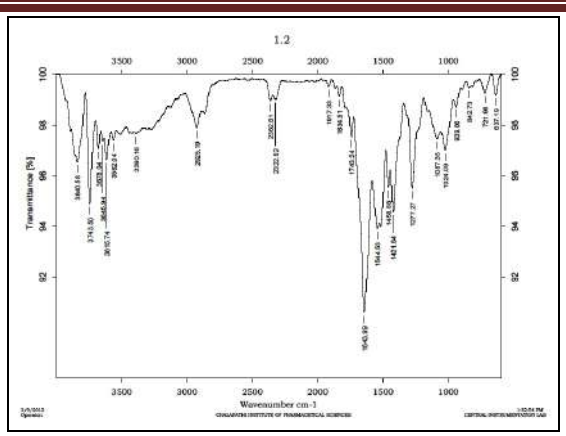


Figure10: Mucoadhesive test data for various prepared formulations



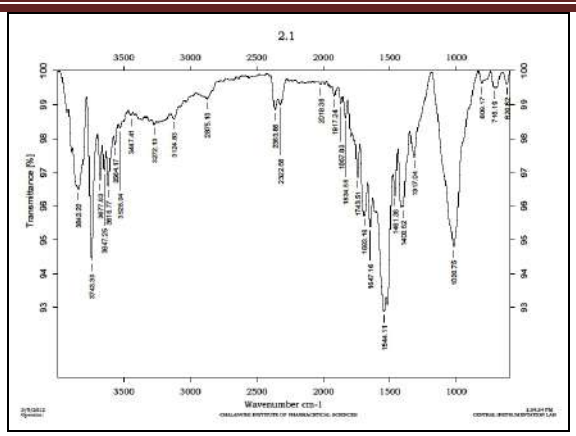
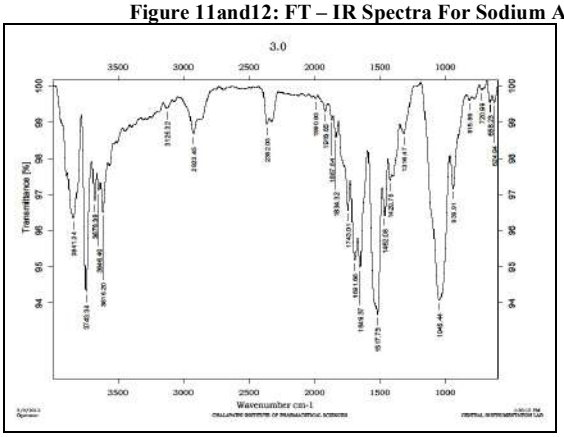


Figure 11and12: FT – IR Spectra For Sodium Alginate: PVP (1:1) and Sodium Alginate: CMC (1:1)



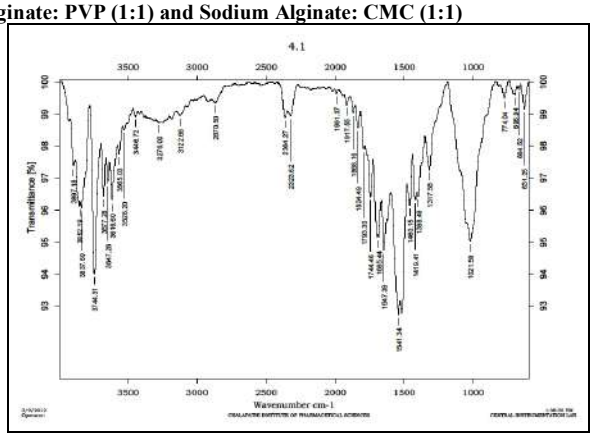


Figure 13 and 14: FT – IR Spectra for Sodium Alginate: SCMC (1:1) and Sodium Alginate: MC (1:1)

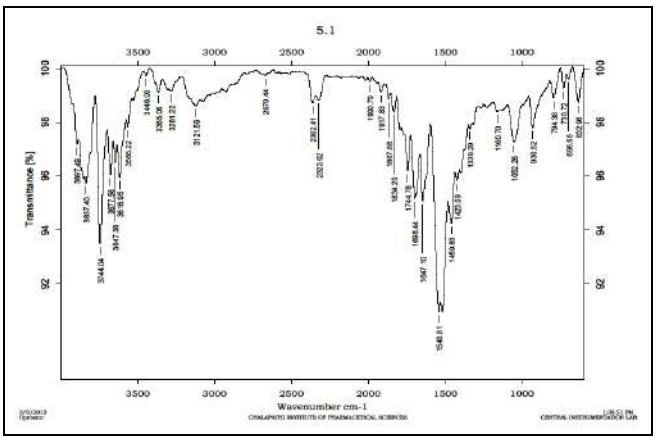
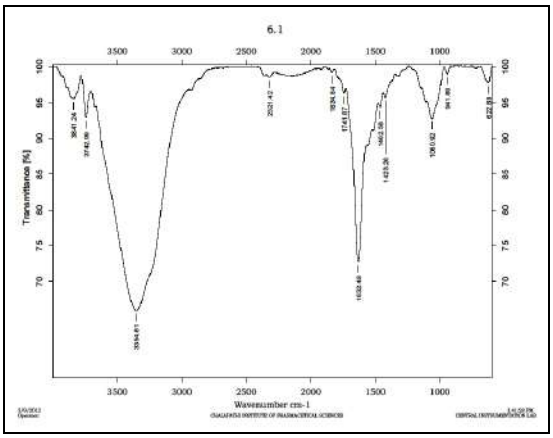


Figure 15: FT – IR Spectra for pure drug (Metformin hydrochloride)



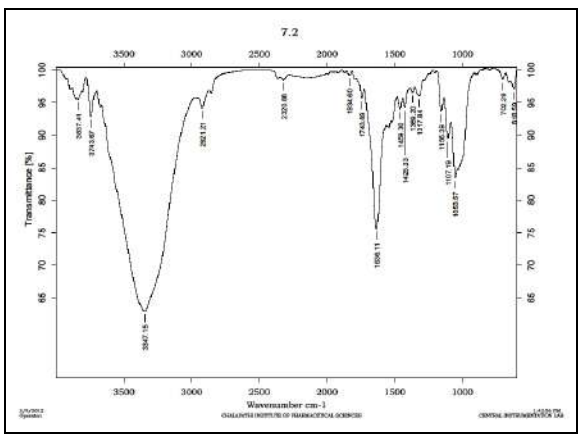


Figure 16 and 17: FT – IR Spectra for M_{11} Formulation and M_6 Formulation

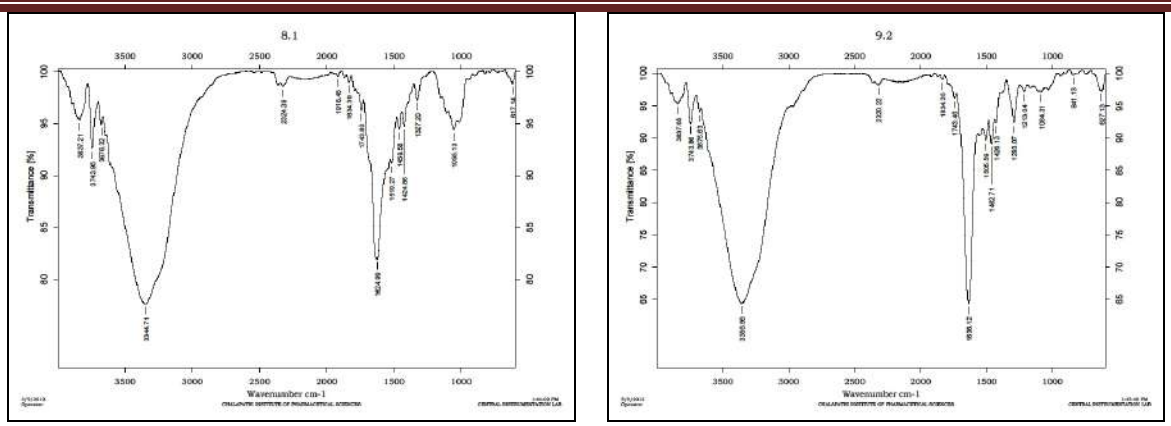


Figure 18 and 19: FT – IR Spectra for M_1 Formulation and M_{16} Formulation

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