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Formulation and Evaluation of Mucoadhesive Microspheres of Ibuprofen by Using Natural and Synthetic Polymers

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I. INTRODUCTION

CONTROLLED DRUG DELIVERY SYSTEM:

Controlled drug delivery systems have acquired a center stage in the area of pharmaceutical research & development sector**.** Such systems offer temporal &/or spatial control over the release of drug and grant a new lease of life to a drug molecule in terms of controlled drug delivery systems for obvious advantages of oral route of drug administration. These dosage forms offer many advantages, such as constant drug level at the site of action, prevention of peak-valley fluctuation, reduction in dose of drug, reduced dosage frequency, avoidance of side effects and improved patient compliance**.**

Oral drug delivery is most desirable method of administering therapeutic agents for their systemic effect. It is considered as the first method of choice in the discovery and development of new drug entities and pharmaceutical formulations because of patient acceptance, convenience in administration and cost-effective manufacturing process.

Oral delivery can be classified into three categories:

- Immediate release – which designed for immediate release of drug for rapid absorption.
- Sustained release – Designed on the basis of spansule coating technology for extended absorption.
- Controlled and targeted DDS – which are more pharmaceutical and clinical superiority over conventional immediate release pharmaceutical products.

The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to achieve promptly and then. Maintain the desired drug concentration that is the drug delivery system should deliver drug a rate detected by the needs of the body over an entire period of treatment. This is possible through administration of conventional dosage from in a particular dose and particular frequency to provide a prompt release of drug. Therefore, to achieve and maintain the concentration within the therapeutically effective range needs repeated administration in a day. This results in a significant fluctuation in a plasma drug level, leads to several undesirable toxic effects, and poor patient compliance.

Recently, dosage forms that can precisely control the release rates and target drugs to a specific body site have made an enormous impact in the formulation and development of novel drug delivery systems. Microspheres form an important part of such novel drug delivery systems. They are designed to control the drug release from the dosage form to improve bioavailability, reduce the adverse action and prolong the action of drug, reduce absorption difference in patients, reduce the dosing frequency and adverse effects during prolong treatment. It is needed to formulate in long-acting dosage form reaching to effective biological site rapidly.

Multiparticulate Drug Delivery System:

Microparticulate drug delivery systems have various well-known advantages over single unit dosage form. Multiple unit dosage forms such as microspheres or micro beads have gained in popularity as oral drug delivery systems because of more uniform distribution of the drug in the gastrointestinal tract, more uniform drug absorption, reduced local systems have various well-known advantages over single unit dosage form.

Multiple unit dosage forms irritation and elimination of unwanted intestinal retention of polymeric material, when compared to non-disintegrating single unit dosage form.

Recently the novel dosage forms which can control the release rate and target the active drug molecule to a particular site.

Microparticulate systems are one of the novel drug delivery system which possess several applications and are made up of with suitable polymer.

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Multiple Unit Dosage Forms
Used in the drug delivery are as follows

- Microgranules
- Pellets
- Microcapsules
- Microspheres
- Microbeads

Micro Granules / Spheroids:

In this drug is wet granulated alone or incorporated into inert granules and then coated to control the release pattern.

Pellets:

Pellets are prepared by coating inert drug pellets with film-forming polymers. The release depends upon the coating composition of polymer and the number of coatings.

Microcapsules:

Microencapsulation is the process of enclosing a substance inside a miniature called capsule. Microcapsules are a small sphere with a uniform wall around it. The material inside the microcapsule is referred to as the core/ internal phase, whereas the wall is sometimes called a shell/coating. The microcapsule size ranges from 1 µm -7 mm.

Microspheres:

Microspheres are small spherical particles, with diameters ranging from 1 µm to 1000 µm. They are free-flowing spherical particles consisting of proteins or synthetic polymers which are biodegradable.

MICROSPHERES:

Microspheres are the bearer connected medication drug delivery framework in which molecule size is ranges from 1-1000 µm extend in breadth having a center of medication and totally external layers of polymer as covering material. In any case, the Achievement of these microspheres is constrained because of their short habitation time at site of ingestion.

It would, in this way be favorable to have implies for giving a cozy contact of the medication drug delivery framework with the retaining layer. This can be accomplished by coupling bio adhesion qualities to microspheres and creating "mucoadhesive microspheres". Mucoadhesive microspheres have points of interest like proficient retention and improved bioavailability of the medications because of a high surface to volume proportion, a substantially more cozy contact with the bodily fluid layer and explicit focusing of medications to the Retention site. The oral course of medicate organization establishes the most advantageous what's more, favored methods for medication Drug delivery to fundamental dissemination of body. microsphere dependent on different Polymers, strategy of readiness of mucoadhesive microspheres, strategy for assessment and their applications in drug delivery. Mucoadhesive microspheres incorporate microparticles furthermore, microcapsules (having a Centre of medication) of 1-1000µm in breadth and comprising either completely of a Mucoadhesive polymer and having an external covering of it, separately. Microspheres, by and large, have the potential to be utilized for focused and controlled discharge medicate drug delivery; yet coupling of bio adhesive properties to microspheres has extra favorable circumstances for example effective ingestion and bioavailability of the Sedates because of high surface to volume proportion, a much increasingly private contact with the mucous layer.

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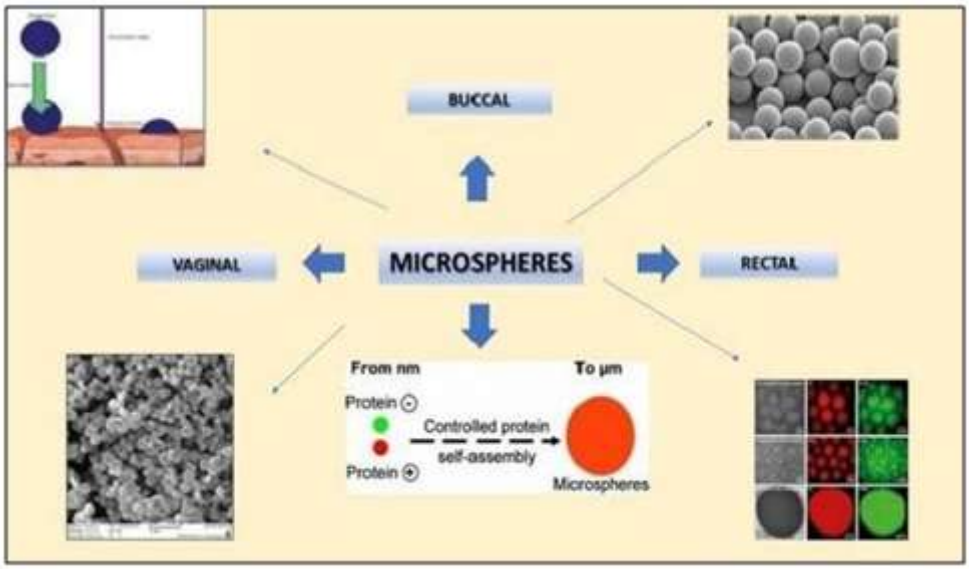
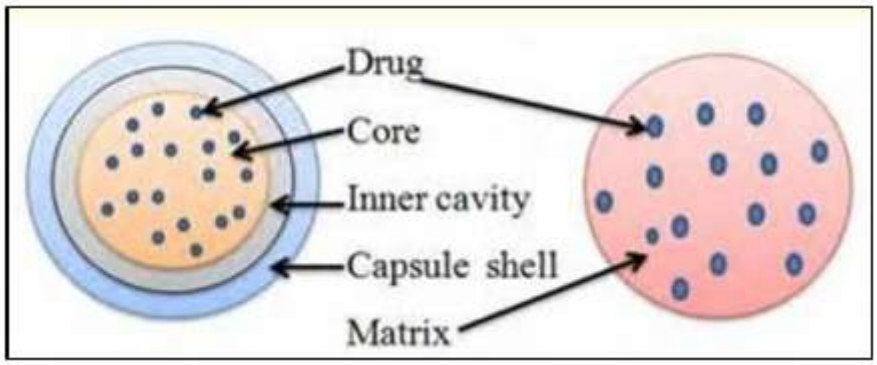


MUCOADHESIVE MICROSPHERES:

Mucoadhesive microspheres incorporate microparticles furthermore, microcapsules (having a Centre of medication) of 1-1000µm in breadth and comprising both definitely of mucoadhesive polymer and having an exterior covering of it, separately. Microspheres, by means of and large, have the doable to be utilized for focused and managed discharge medicate drug delivery; but coupling of mucoadhesive microspheres as an extra advantages. Application of mucoadhesive microspheres to the mucosal tissues of ocular cavity, gastric and colonic epithelium is used for administration of release of localized action. Prolonged launch of capsule and a reduction in frequency of drug.



Administration to the ocular cavity can highly improve the affected person compliance. The latter can be additionally be got for drugs administered intra-nasally due to the reduction in mucociliary clearance of capsules adhering to nasal mucosa. This uptake mechanism has been used for the transport of protein and peptide drugs, antigens for vaccination and plasmid DNA for gene therapy. The thought of a non-invasive single of vaccine, via skill of mucosal.

Immunization, affords controlled release of antigens and as a consequence type some other super utility of mucoadhesive microspheres.

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RAW MATERIALS:

S. No	NAME OF MATERIALS	NAME OF SUPPLIERS
1	Ibuprofen	Caplin point Pvt. Ltd., Puducherry.
2	Sodium alginate	Loba chemie Pvt, Ltd., Mumbai.
3	Polycaprolactone	Carbanio chemical shop.
4	HPMC	Caplin point Pvt. Ltd., Puducherry.
5	Sodium CMC	Loba chemie Pvt, Ltd., Mumbai.
7	Ethyl cellulose	Loba chemie Pvt, Ltd., Mumbai.
8	Calcium Chloride	Loba chemie Pvt, Ltd., Mumbai.

Table No.1: List of raw materials with name of their suppliers.

EQUIPMENTS / INSTRUMENTS USED IN THE STUDY:

S. NO	EQUIPMENTS	MANUFACTURER / SUPPLIERS
1.	Electronic weighing balance	Wensar.
2.	Fourier Transform Infrared Spectroscopy	SHIMADZU.
3.	UV-Visible Spectrophotometer	LabIndia - UV 3000.
4.	Melting Point Apparatus	Guna Enterprises, Madras.
5.	Magnetic Stirrer	Remi Equipments.
6.	Sonicator	Sonica Ultrasonic Cleaner –Model 2200 MH.
7.	Scanning electron microscope	Hitachi, Japan.
8.	Particle size analyzer	Malvern Instruments
9.	Dissolution test apparatus	Lab India
10.	Hot air oven	Labtech Instruments
11.	Stability Chamber	Labtech Instruments
12.	pH meter	Infra Digi Equipments
13.	Zeta sizer	Horiba Scientific
14.	Disintegration test apparatus	Remi Instruments

Table No.2: Equipments used in the formulation and evaluation of Microspheres.

Formulation of Mucoadhesive Microspheres

INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8	F9
IBUPROFEN	1	1	1	1	1	1	1	1	1
SODIUM ALGINATE	1	1	0.8	1	0.8	1	0.8	1	0.8
POLYCAPROLACTONE	-	1	0.2	-	-	-	-	-	-
SODIUM CMC	-	-	-	1	0.2	-	-	-	-
HPMC	-	-	-	-	-	1	0.2	-	-

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ETHYL CELLULOSE	-	-	-	-	-	-	-	1	0.2
CALCIUM CHLORIDE	10% w/v	10% w/v	10% w/v	10% w/v	10% w/v	10% w/v	10% w/v	10% w/v	10% w/v

PROCEDURE:

Ionotropic Gelation Method:

- Orifice Ionotropic gelation method was used for the preparation of alginate microspheres using polymers such as Sodium alginate, Polycaprolactone, Sodium CMC, HPMC and Ethyl cellulose.
- A homogenous polymer solution was prepared by dissolving Sodium alginate and the polymers in purified water.
- Then drug, the active substance was added to polymer solution and stirred thoroughly to form viscous dispersion.
- The total drug and polymers mixture was kept on magnetic stirrer for 1 hr at 700 rpm to obtain a homogenous mixture of desired viscosity to pass easily through the syringe dropper.10% w/v calcium chloride solution was prepared which has been used as a cross linking agent. The prepared dispersion was then manually added drop wise into calcium chloride (10% w/v) solution with the help of syringe having needle of size no.18.
- The calcium chloride solution having the droplets was then allowed to stay for 15 minutes for the curing reaction to take place and produce spherical rigid drug loaded spheres. The spheres obtained after the reaction were then collected and washed repeatedly with water.
- After washing, it is required to dry the spheres properly at 45^0 C for 12 hours.

Preparation of microspheres using Ionotropic Technique

Evaluation of Microspheres:

Percentage Yield:

The percentage yield of mucoadhesive microspheres of Ibuprofen were found to increase as the polymer ratio was also increased. The maximum yield of microspheres were found in F6 formulation – 92.91%.

Table : Percentage Yield:

	Formulation Code (F1 – F9)	Percentage Yield (%)
1	F1	81.36 %
2	F2	73.31 %
3	F3	68.20 %
4	F4	81.92 %
5	F5	84.02%
6	F6	92.91 %
7	F7	89.12 %
8	F8	79.03 %
9	F9	82.06%

Estimation of Drug Content:

The Drug Content of Controlled release microspheres were found to increase as the polymer ratio was increased. Drug content was high in F6 formulation that compared to all formulations. All the formulations Drug content data was showed in table

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S. No.	Formulations	Drug Content*
1	F1	80.49
2	F2	77.27
3	F3	70.21
4	F4	87.89
5	F5	91.24
6	F6	96.56
7	F7	89.86
8	F8	76.67
9	F9	84.39

Drug Entrapment Efficiency:

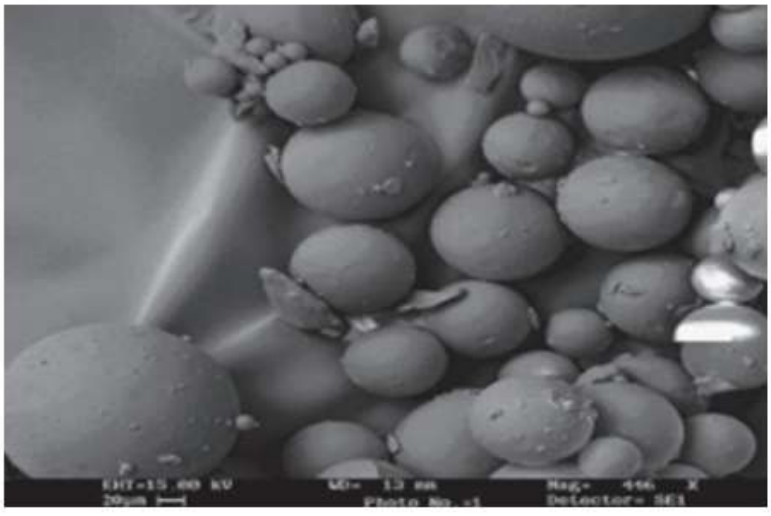
The Drug Entrapment Efficiency of Controlled release microspheres were found to increase as the polymer ratio was increased. Entrapment Efficiency was high in F6 formulation that compared to all formulations. All the formulations Drug Entrapment Efficiency data was showed in table

S.NO	Formulations	Entrapment Efficiency
1	F1	59.99
2	F2	51.79
3	F3	48.32
4	F4	65.58
5	F5	54.13
6	F6	68.58
7	F7	60.14
8	F8	63.85
9	F9	61.42

Scanning Electron Microscopy (SEM):

Surface morphology and shape characteristics of microspheres were evaluated by means of scanning electron microscopy. The surface morphology of optimized best formulation (F9) shows the photomicrographs at different magnifications and voltages.

SEM photographs of the microspheres revealed that the microspheres were spherical with smooth surface nature and no aggregation were showed in following figures.



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Swelling Study/Degree of swelling:

Swelling study of Ibuprofen mucoadhesive microspheres were performed in pH phosphate buffer up-to 8 hours. It was represented in table 9.13 and showed in Figure 9.18.

Table : Data of Swelling Test:

S. No	Hours	In 0.1N HCl (%)			In pH 6.8 Phosphate Buffer (%)		
		F4	F6	F7	F4	F6	F7
1	1	8	10	9	8	12	10
2	2	14	20	18	18	23	19
3	3	20	32	28	27	34	26
4	4	28	43	32	38	45	37
5	5	32	50	42	52	58	43
6	6	43	56	51	58	64	55
7	7	50	58	54	63	72	68
8	8	57	62	60	72	79	73

Mucoadhesion Testing / In-vitro Wash off Test:

The in-vitro wash off test for mucoadhesive for all formulations (F1 to F9) was studied in 0.1N HCl and pH 6.8 phosphate buffer. The result of in-vitro wash off test data were represented in table 9.14.

Table : Mucoadhesion Testing 0.1N HCl

Time	F1	F2	F3	F4	F5	F6	F7	F8	F9
1 hr	78	58	64	70	75	67	54	54	85
2 hr	68	42	54	62	66	58	42	38	72
3 hr	60	32	42	54	51	42	34	29	63
4 hr	55	26	33	40	43	31	12	13	54
5 hr	44	15	24	29	36	27	-	-	47
6 hr	39	8	13	17	28	18	-	-	39
7 hr	25	-	-	10	13	9	-	-	25
8 hr	9	-	-	-	6	-	-	-	12

Table : Mucoadhesion Testing in pH 6.8 Phosphate Buffer

Time	F1	F2	F3	F4	F5	F6	F7	F8	F9
1 hrs	78	56	60	70	75	65	50	54	80
2 hr	69	46	50	61	67	51	38	40	71
3 hr	55	35	47	53	51	43	21	21	61
4 hr	43	26	38	45	43	35	10	10	51
5 hr	35	14	29	34	36	28	-	-	42
6 hr	25	-	15	21	28	20	-	-	32
7 hr	12	-	-	9	14	12	-	-	25
8 hr	-	-	-	-	-	-	-	-	10

Microspheres with a coat consisting of sodium alginate and a mucoadhesive polymer exhibited good mucoadhesisve properties in the in-vitro wash-off test.

The result of in-vitro wash-off test studies indicate that the formulation F6, having good mucoadhesive property with more retention time in pH 6.8 phosphate buffer and in 0.1N HCl than other formulation.

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In-vitro Drug Release Study:

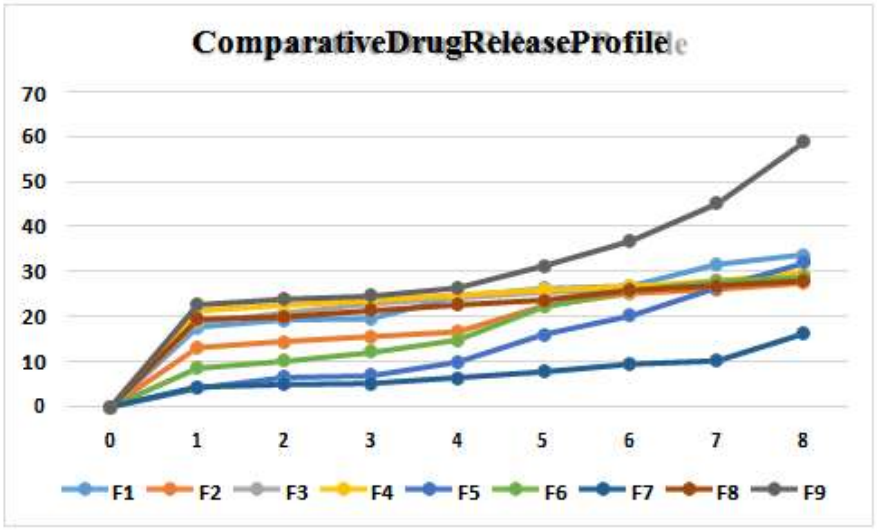
In-vitro drug released profiles of Ibuprofen microspheres were performed in pH 6.8 phosphate buffer up-to 8 hours. It was represented in table 9.17 and showed in Figure

Table : Parameters were used for the dissolution study

Apparatus	USP Type I apparatus (Basket type)
Temperature	37 ± 0.5^{0}C
Total volume	900 ml
Speed	100 rpm
Drawn volume	5 ml
Running time	8 hours
Dissolution Medium	pH 7.2 phosphate buffer

Table : Percentage Drug Release of Formulation F1-F9

Time (hr)	Percentage Drug Release (%DR)*								
	F1 DR%	F2 DR%	F3 DR%	F4 DR%	F5 DR%	F6 DR%	F7 DR%	F8 DR%	F9 DR%
1	11.97	9.68	7.12	16.42	14.53	18.71	15.88	14.67	14.94
2	21.00	20.06	18.44	28.01	23.16	29.35	25.85	23.29	22.08
3	27.20	26.66	24.77	38.51	34.74	42.56	37.98	29.22	31.24
4	39.19	37.03	33.53	51.58	46.73	54.82	48.22	41.48	44.58
5	45.39	43.90	38.92	62.23	52.12	65.06	55.09	47.27	49.70
6	53.74	51.04	49.43	70.04	57.78	73.14	64.79	55.36	57.51
7	64.38	62.77	56.70	76.51	68.83	80.55	72.74	63.44	65.86
8	70.31	69.91	64.11	84.59	79.34	89.17	81.22	73.95	76.10



II. SUMMARY AND CONCLUSION

The goal of any drug delivery system was to provide the therapeutic amount of drug to the proper site in the body also to achieve and maintain the desired drug concentration in blood. Improving the therapeutic efficacy of existing drugs has been tried by different technologies. One of the effective technologies exiting in recent years of pharmacy is microspheres.

The mucoadhesive drug delivery system was a new approach in pharmaceutical field and drug retention for a prolonged time has been achieved. Hence, it was made an effective attempt

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to formulate the mucoadhesive microspheres by Ibuprofen as the model drug.

Ibuprofen is a HMG-CoA Reductase inhibitors (statins) used in the treatment of hypercholesterolemia or hyperlipidemia. Rosuvastatin calcium is widely prescribed by physician and bioavailability of Rosuvastatin calcium was 20 % .Hence, the drug Rosuvastatin calcium for designing of mucoadhesive microbead in order to improve the bioavailability by prolonging the drug release at specified time period.

Mucoadhesive microspheres of Ibuprofen were successfully prepared by Ionotropic gelation technique was confirmed that it was a best method for preparing microbeads from other methods. Because, it's give higher percentage yield.

The identification of drug was carried out by FT-IR spectroscopy, identification test and melting point. The physicochemical parameters such as appearance, solubility study and loss on drying were performed by suitable methods. The analytical profile of drug was evaluated for determination of absorption maximum, development of standard curve and percentage purity of drug.

Compatibility of drug and polymer mixture was done by performing FT-IR study. It was concluded that there was no interaction between the drug and polymer.

Mucoadhesive microspheres were obtained by ionotropic gelation method for all the formulations from F1 to F9. Formulations F1 to F9 were prepared with different concentration of polymer and with constant drug ratio of Ibuprofen.

Based on all the above evaluation parameters it was concluded that the formulation F6 was found to be best formulation among the formulations from F1 to F9. The in-vitro drug released data was applied to various kinetic models such as zero order kinetics, Higuchi plot, first order kinetics and Peppas plot for predict the drug release kinetics mechanism. The formulation F6 was best fitted with zero order kinetics followed by super case II transport (n>1.0).

According to stability study it was found that there was no variation in drug content, entrapment efficiency, and in-vitro drug released profile of optimized formulation F6 for 3 months period.

From the overall studies it can be concluded that the **formulation F6** considered as the best formulation among nine formulations by comparing all the evaluated parameters.