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Formulation and evaluation of novel multi particulate drug delivery system.

Author: Vishwajeet G. Thorat
Corresponding author: Ashish P. Yewatkar, Mayuri S. Pahurkar

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ABSTRACT : A novel multiparticulate drug delivery system was formulated. Prednisolone microspheres were formulated using tamarind gum powder as a natural polymer. The formulation was designed with aim of reducing disadvantages of single unit formulation and better control over the formulation characteristics. Tamarind gum microspheres were prepared by emulsion dehydration method using polymer in ratio of 1:1 to 1:9. The prepared microspheres were evaluated for average particle size, percentage yield, drug entrapment efficiency and in vitro drug release. The size of microspheres was observed in range of 42 µm to 89 µm, the drug entrapment efficiency was found in range of 32.12-83.98% .Drug release studies show gradual rise in percent release where 85% of drug releases after 8hrs. The various formulation variables were optimized for desired characters and tamarind gum powder showed the potential for formulation of microspheres.

KEYWORDS : Microspheres, Prednisolone, Tamarind gum , Emulsion dehydration

I. INTRODUCTION :

The majority of multi-particulate drug delivery methods are oral dosage forms made up of numerous tiny discrete units, each of which possesses a variety of desired properties. These systems divide the medication dosage into many subunits, often made up of thousands of spherical particles having a diameter of 0.05 to 2.00 mm [(1)]. A multiparticulate drug delivery system's primary goal is to maintain the highest possible plasma drug concentration, which improves the medicine's effectiveness, safety, and bioavailability while also increasing patient compliance. [(2)] Pharmaceutical research & development is currently moving forward and concentrating on the best way to distribute medications so as to maximise their therapeutic effects while reducing their side effects. The therapeutic efficacy of a specific drug is increased by controlled drug delivery systems, which release the drug at a controlled rate while resolving the issues with conventional drug delivery systems. [(2)]

TYPES OF MULTIPARTICULATE DRUG DELIVERY SYSTEM [(1,2,3)] :

1. Pellets
2. Minitab lets
3. Spheroids
4. Granules
5. Microspheres
6. Nano spheres

ADVANTAGES AND DISADVANTAGES [(2,4)]:

ADVANTAGES	DISADVANTAGES
Dose dumping is avoided.	Drug loading is low.
Faster gastric emptying than tablets.	Higher need of excipients.
Less local irritant and Distribution is better.	Huge number of process variables.
Better stability and Desired drug release	Many formulations steps.
Flexibility in design.	Huge cost of production.
Increased in Bioavailability.	Advance technology is needed.
Reduced Adverse effects	Trained and skilled person needed.

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Advantages of microspheres over conventional dosage forms [5,6,7]:

- A consistent and extended therapeutic impact is provided by microspheres.
- Especially when used with a buffer, microspheres offer independence from drug and recipient incompatibilities.
- The use of microspheres prevents dosage dumping.
- Drugs are protected from the environment by microspheres.
- Microspheres also cover up flavours and odours.
- Microspheres avoid the initial metabolic process.
- Microspheres are small and spherical in shape, making it simple to inject them into the body. Microspheres boost both the bioavailability and the biological half-life.
- Additionally, microspheres lessen the possibility of G.I. discomfort.
- Microspheres lessen the need for frequent dosing, which enhances patient compliance.
- Microspheres distribute the medicine in a controlled, sustained, and targeted manner.
- Microspheres result in more consistent medication absorption.
- Drug discharge in the stomach is prevented, which lessens the likelihood of local side effects.
- Microspheres can improve the therapeutic effect of drugs with short half-lives..

Disadvantages of microspheres [5,6] :

- Microspheres are expensive.
- Less reproducibility; possible effects on the stability of core particles from process variables like temperature, pH, and solvent addition.
- It requires a particular magnet for targeting, cutting-edge tools for monitoring, and qualified individuals to carry out treatments because polymers might have harmful effects, such as polyvinyl chloride.

II. MATERIAL AND METHOD :

Drug Profile

Prednisolone [8]:

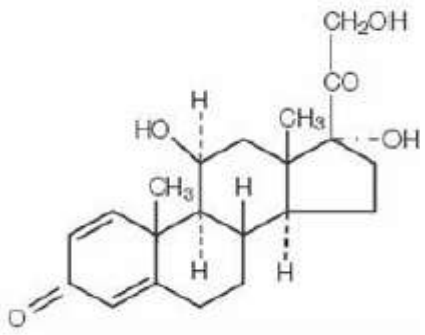

Fig. Structure of prednisolone

IUPACName:11,17-Dihydroxy-17-(2-hydroxyacetyl)-10,13-dimethyl-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydrocyclopenta[a] phenanthren-3-one.

Table : Profile of prednisolone :

Molecular formula	$C_{21}H_{26}O_5$
Molecular weight	360.4
Appearance	White , Amorphous powder
Solubility	Slightly soluble in water, soluble in 27 parts of absolute ethanol, in 30 parts of ethanol, in 50 parts of acetone, and in 180 parts of chloroform. It is soluble in dioxane and methanol.
Category	Corticosteroids

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POLYMER PROFILE:

❖ Tamarind gum powder [9,10]

Synonyms:, Imlee, Imli, Tamarin, Tamarindo, Tamarindusindica, Tamarinier.

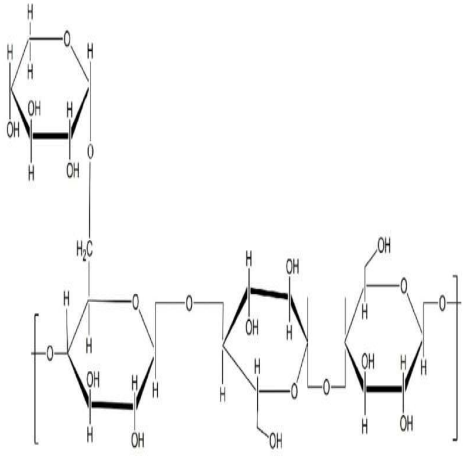

Fig., Chemical structure of tamarind gum

Molecular Formula: C8H24
Molecular weight: 52350 units
Solubility: Tamarind gum is soluble in hot water. It requires heating to fully solubilise.

Extraction of tamarind gum polymer:

The tamarind gum seeds were bought at the neighbourhood market. By drying the tamarind seeds in a hot air oven for 20 minutes at 40 °C, the testa was removed. The seed coat was then simply crushed off of the seed. The isolation technique was then applied to the obtained white portions of the seeds.. Put enough of the tamarind gum powder in a beaker. With the aid of a glass rod, swirl some water into a beaker. Overnight, let the solution stand. The following day, add some water and mix one more. Utilizing a muslin cloth, filter the mixture, then gather the tamarind gum extract. The extract is then dried in a hot air furnace to create powder.

Characterization of tamarind gum powder:

The tamarind gum was characterized for following properties.

1) Organoleptic properties
2) Swelling index
3) Bulk density
4) Tap density
5) Compressibility index and hausner ratio
6) Melting point

Preformulation studies of prednisolone :

Determination of melting point:

Melting point of prednisolone was determined by capillary method.

Solubility :

Solubility of prednisolone was determined in different solvents in separate beaker.

Determination of λ_{max} :

A stock solution of prednisolone was prepared by using phosphate buffer of pH 6.8.and the sample was scanned under UV in range of 200-400 nm.

Preparation of standard curve of prednisolone [11] :

A pH 6.8 phosphate buffer was made and filtered. Prednisolone was dissolved in 100 ml of pH 6.8 phosphate buffer in a calibrated flask at a concentration of 0.1 gm. After diluting the solution from 1 millilitre to 10 millilitres in a calibrated flask, a succession of 10 millilitre calibrated flasks are then pipetted with 1 to 5 millilitres of the standard drug solution (100ug/ml). At a wavelength of 243 nm, the absorbance of this solution is measured in comparison to a reagent blank.

Preparation of Phosphate buffer pH 6.8[12]: In a 200 ml calibrated flask, combine 50 ml of 0.2 M potassium dihydrogenphosphate with 22.4 ml of 0.2 M sodium hydroxide, then fill the remaining space with distilled water.

Determination of IR spectrum:

A FTIR spectrophotometer was used to measure the drug's IR spectra between 700 and 1000 nm.

X ray crystallography: The crystallographic structure of prednisolone was determined by XRD.

Formulation of prednisolone microspheres [11] :

Based on the emulsion dehydration procedure, prednisolone microspheres were created. Prednisolone microspheres were made in various batches by adjusting the medication and polymer concentrations. The 10ml of distilled water is mixed with the drug polymer dispersion. This mixture was added to 15ml of 1% span 80-containing soybean oil. To create a stable emulsion, the resulting emulsion was agitated using a magnetic stirrer. The tamarind gum droplets were dehydrated by adding 50ml of acetone, which was then completely evaporated over the course of two hours of continuous stirring at 1000 rpm. The mixture was filtered through muslin cloth, and the

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resulting microspheres were dried and cleaned with acetone.

Formulation	Drug : polymer	Stirring speed (Rpm)	W/O ratio	Oil used
F1	1:2	1000rpm	1:1.5	Soyabean oil
F2	1:3	1000rpm	1:1.5	Soyabean oil
F3	1:4	1000rpm	1:1.5	Soyabean oil
F4	1:5	1000rpm	1:1.5	Soyabean oil
F5	1:6	1000rpm	1:1.5	Soyabean oil
F6	1:7	1000rpm	1:1.5	Soyabean oil
F7	1:8	1000rpm	1:1.5	Soyabean oil
F8	1:9	1000rpm	1:1.5	Soyabean oil

Evaluation of prednisolone microspheres [11,13, 14] :

The prepared microspheres are characterized and evaluated for following parameters.

Percentage yield (%)

By dividing the actual weight of the product by the sum of all the non-volatile ingredients used in the manufacturing of the microspheres, the percentage yield of the product was computed.

% yield = weight of microspheres / weight of drug and polymers * 100

Particle size analysis [11]

Optical microscopy was used to determine the microspheres' particle size and shape. A stage micrometre and an ocular micrometre that had been previously calibrated were used to measure the microspheres' horizontal diameters as they were being examined under an optical microscope. Each formulation contained about 100 particles, which were counted and measured.

Surface morphology [15]

Optical microscopy was used to determine the microspheres' particle size and shape. A stage micrometre and an ocular micrometre that had been previously calibrated were used to measure the microspheres' horizontal diameters when they were being inspected under an optical microscope. Each formulation had about 100 particles, which were counted and measured.

Drug Entrapment Efficiency [16]:

By sonicating 500 mg of microspheres in 100 ml of 0.2 M phosphate buffer pH 6.8, the effectiveness of drug entrapment was assessed. The filtrate was spectrophotometrically analysed at 243 nm after 24 hours. The calibration plot was used to calculate the drug content in the sample and the effectiveness of drug entrapment.

% Drug Entrapment = Calculated drug concentration/ Theoretical drug concentration× 100.

In vitro Drug Release Studies [12, 16] :

Using a US Pharmacopoeia paddle type-II dissolution equipment at 37 0.5 oC with a constant stirring rate of 100 rpm, in vitro drug release tests were conducted. Microspheres weighing 100 mg were employed for the test. An accurately weighed sample was placed in 900 ml of pH 6.8 phosphate buffers and allowed to dissolve for eight hours. At regular intervals of one hour, a 1 ml sample volume was taken out and replaced with a fresh 1 ml of

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dissolving medium. The sample underwent filtering and 243 nm spectrophotometric analysis.

III. RESULTS AND DISCUSSION :

Sr no	Characteristics	Results
1	Colour	Pale yellow
2	Odour	Characteristics
3	Taste	Bitter
4	Swelling Index	81.83%.
5	Bulk density (g/cm3)	0.80 g/cm^2
6	Tapped density(g/cm3)	0.83 g/cm^2
7	Compressibility index	3.61
8	Hausner ratio	1.037
9	Total Ash Value	15.9%

Solubility of tamarind gum: It is soluble in hot water, Insoluble in ethanol, Insoluble in benzene and Insoluble in Acetone.

Melting point of tamarind gum: Tamarind gum was found to have a melting point between 248 and 254 °C.

Identification of drug

Determination of melting point:

Prednisolone's melting point was established using the capillary method. Prednisolone's melting point was discovered to be between 230 and 235 °C, which met IP standards.

Solubility: Water, ethanol, acetone, and chloroform are all just very slightly soluble in it.

Sr no.	Conc (ug/ml)	Absorbance
0	0	0
1	2	0.216
2	4	0.429
3	6	0.619
4	8	0.831
5	10	1.001

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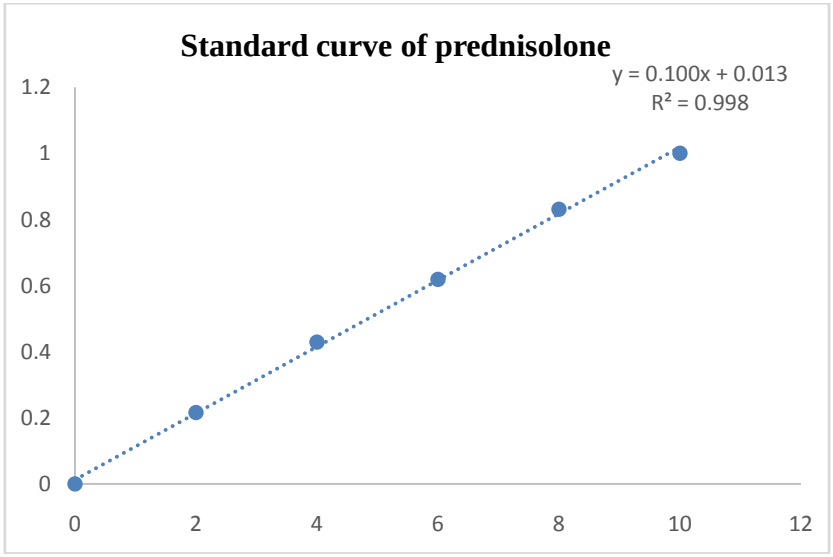

Fig Standard calibration curve of prednisolone

Standard calibration curve of prednisolone :

Prednisolone stock solution is created and examined at 243 nm in phosphate buffer solution with pH 6.8. The data were subjected to linear regression analysis after the graph of absorbance v/s concentration was generated. Prednisolone's standard calibration curve was a straight line. With passing time, there is an increase in absorption. Therefore, the standard curve adheres to Beer's and Lambert's law.

Compatibility studies (IR and XRD)

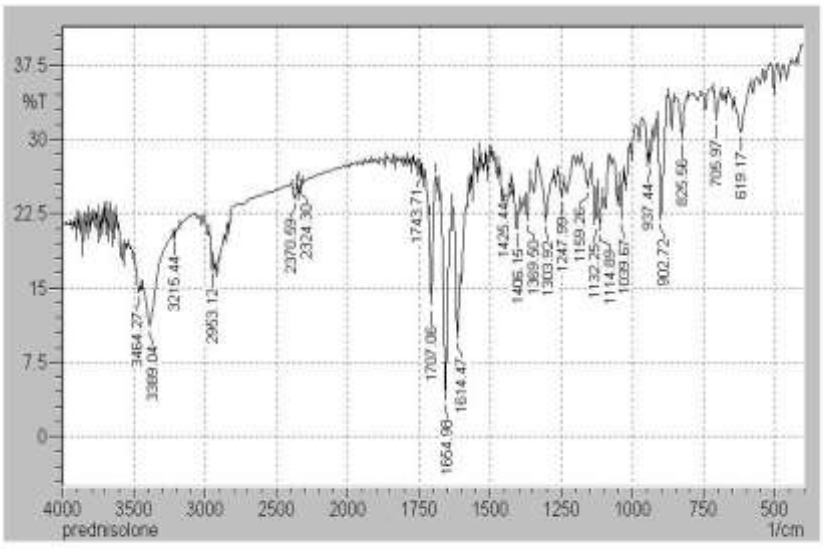

Fig. IR- spectra of pure drug prednisolone

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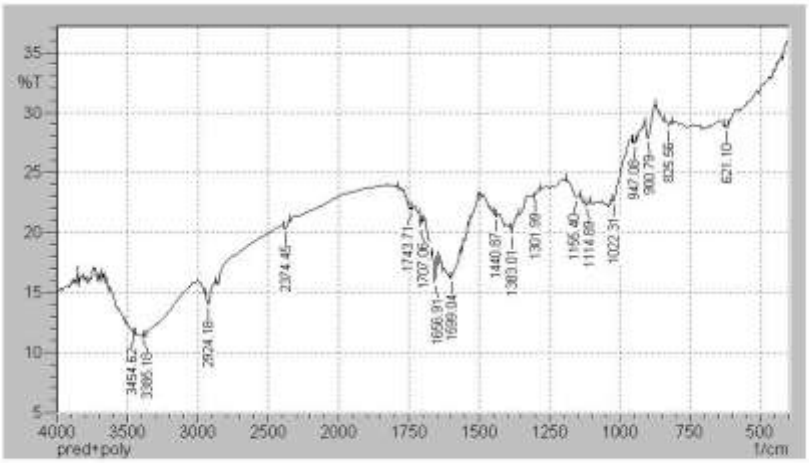

Fig., IR – spectra of prednisolone – tamarind gum

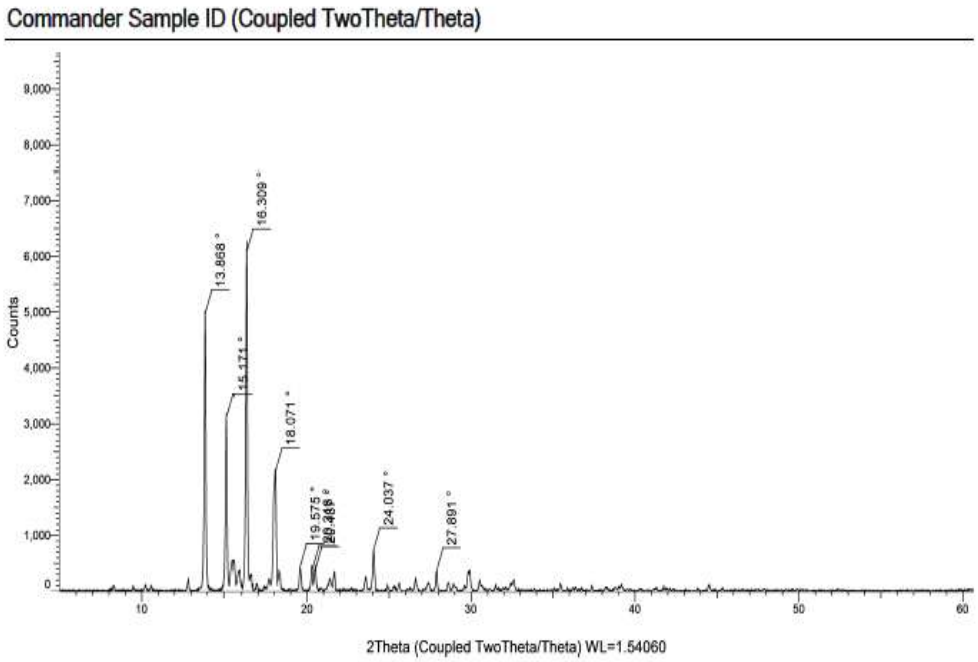

Fig. ,XRD of pure drug prednisolone

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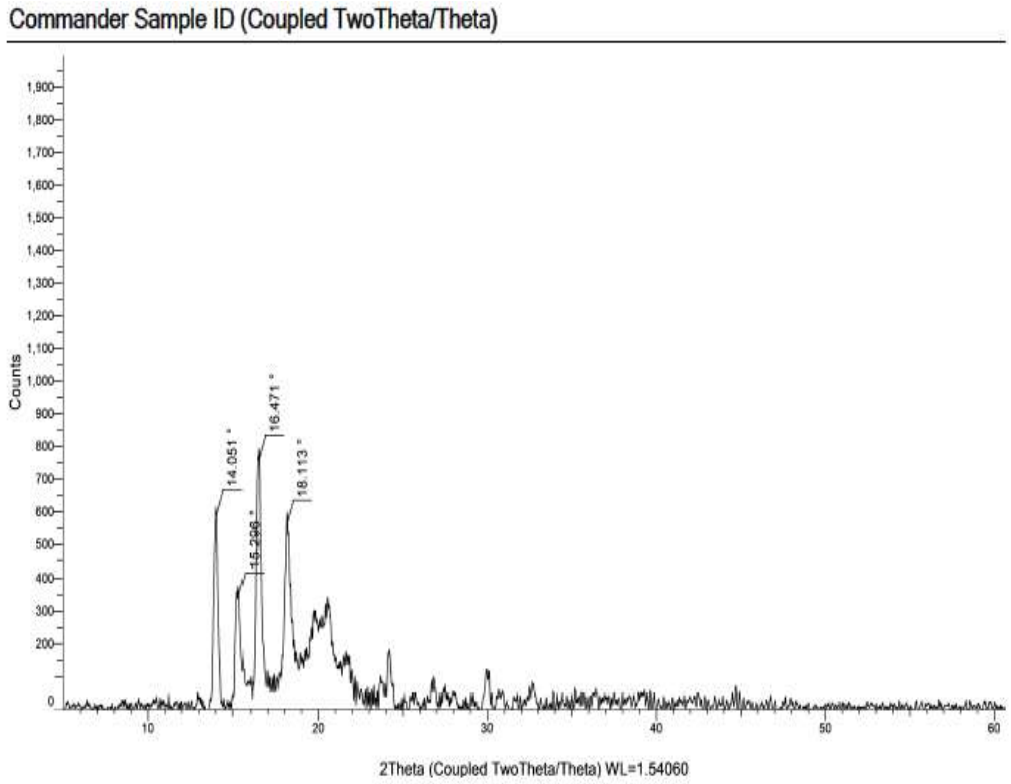

Fig. XRD of prednisolone and tamarind gum

The current study examined the IR spectra and XRD of pure medication and polymer, and it was found that there is no chemical interaction between prednisolone and polymer. The primary peak of the IR and XRD spectra of the medication and polymer mixture did not change, indicating that there was no physical interaction due to the bond formation between the two substances.

Characterization of microspheres

Table , Characterization of microspheres of prednisolone

Formulation	Percentage yield (%)	Avg particle size (µm)	Drug entrapment efficiency (%)
F1	72	42	32.12
F2	77	49	45.02
F3	78	55	49.61
F4	91	89	83.98
F5	84	74	59.18
F6	85	79	62.30
F7	88	83	65.74
F8	89	85	69.81

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Percentage yield

Prednisolone microspheres' yield as a percentage was determined to be between 72 and 91%. It was found that the product yield increases when the polymer content in the formulation rises. The average percentage yield was found to be greater than 50% across all batches, demonstrating the viability of this technology for creating microspheres. The highest yield is in batch F4, which is 91%. The results are displayed in the table above.

Particle size

For formulations F1, F2, F3, and F4, the average particle size range was found to be 42 m, 49 m, 55 m, and 89 m, respectively. For formulations F5, F6, and F7, the average particle size range was found to be 74 m, 79 m, 83 m, and 85 m, respectively. The highest yield is in batch F4, which is 91%. With an increase in polymer concentration, microsphere particle size increases.

Surface morphology using SEM

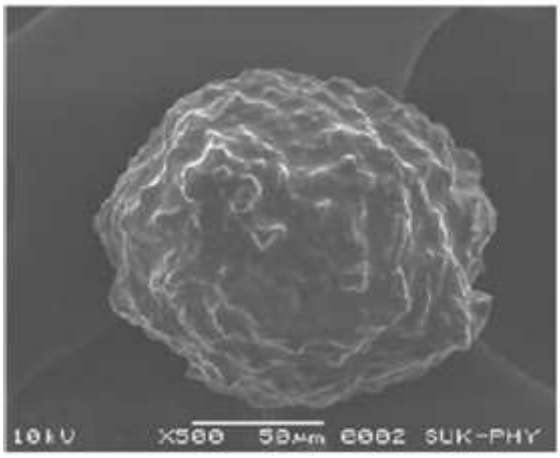

Fig., SEM of uncoated prednisolone microspheres

Scanning electron microscopy was used to analyse the morphology of microspheres. The prepared microspheres had size in micrometres, and the SEM investigation revealed that the particles were almost spherical.

In vitro Drug Release Studies:

	Cumulative %Drug release							
Time interval	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
0hr	0	0	0	0	0	0	0	0
1hr	30	25	22	32	18	15	12	11
2hr	39	29	24	44	21	19	16	14
3hr	41	36	35	46	26	21	19	17
4hr	58	52	46	59	36	31	30	29
5hr	67	59	52	70	41	36	33	29
6hr	74	71	62	78	51	44	36	32
7hr	78	70	66	81	58	51	42	39
8hr	82	75	69	85	64	62	56	51

Table . Cumulative drug release with respect to time

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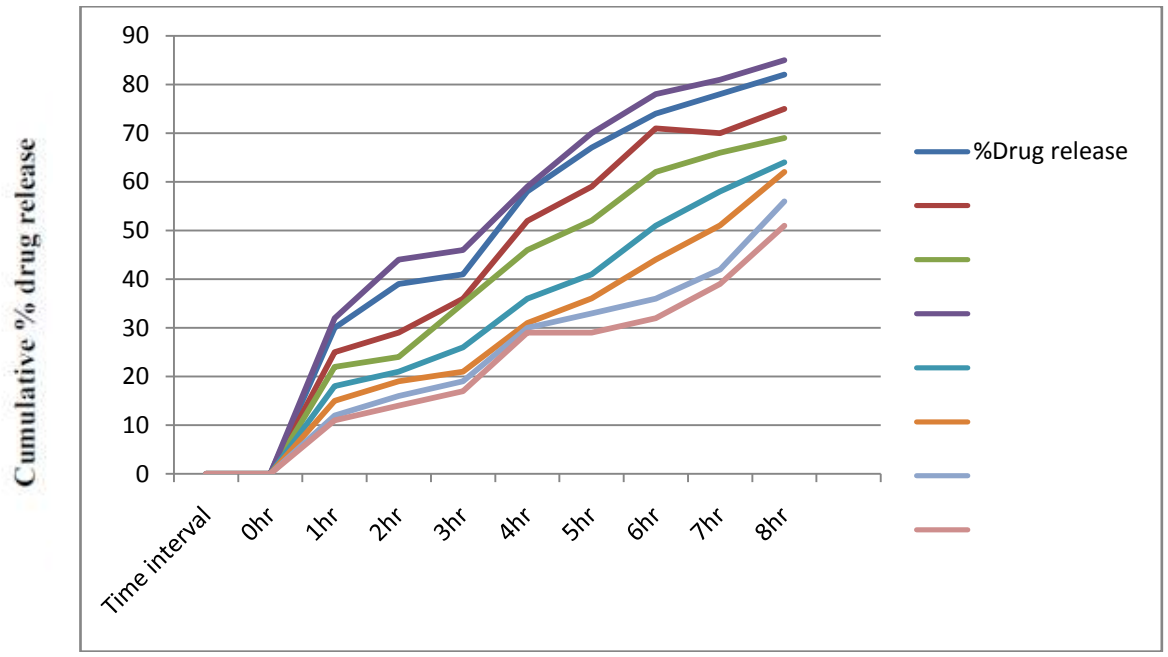

Fig, 9.7 Time Vs cumulative % drug release of prednisolone microspheres

Prednisolone microspheres were given an in vitro drug release in phosphate buffer at pH 6.8. On in vitro drug release, the impact of tamarind gum concentration was seen. Drug release rates in formulations F1, F2, F3, and F4 were respectively up to 82%, 75%, 69%, and 85%. The percentage of drug release in formulations F5, F6, F7, and F8 was 64%, 62%, 56%, and 51%, respectively. In a phosphate buffer at pH 6.8, prednisolone release from tamarind gum microspheres was greater in formulation F4.

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