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FORMULATION AND EVALUATION OF ASPIRIN MICROSPHERES BY COACERVATION PHASE SEPARATION METHOD

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ABSTRACT

The present study focuses on the formulation and evaluation of aspirin microspheres using the coacervation phase separation method. Gelatin and gelatin–carbopol polymer combinations were utilized in six formulations (F1–F6) to optimize microencapsulation efficiency, flow properties, and drug release performance. Microspheres were prepared by thermal-induced coacervation followed by cross-linking using glutaraldehyde. The prepared microspheres were evaluated for particle size, drug entrapment efficiency, pre-compression parameters, in-vitro drug release, infrared spectroscopy, and assay by HPLC. The mean particle size across all formulations predominantly ranged around 850 µm, indicating uniformity. Flow properties such as bulk density, Carr's index, Hausner's ratio, and angle of repose were within acceptable limits, confirming good micromeritic behavior. IR spectroscopy confirmed the absence of interactions between aspirin and the polymers. Drug release studies revealed controlled release, and among all formulations, F3 exhibited optimal characteristics in terms of entrapment efficiency, flow properties, and dissolution profile. Overall, the study demonstrates that coacervation is an effective technique for developing controlled-release aspirin microspheres suitable for further development.

KEYWORDS: Aspirin, Microspheres, Coacervation, Gelatin, Carbopol, Controlled Release, Entrapment Efficiency, HPLC Analysis, Micromeritics, Phase Separation.

1. INTRODUCTION

Controlled drug delivery systems are designed to optimize therapeutic outcomes by maintaining drug concentrations within the desired therapeutic window for extended periods. Microspheres represent one of the most effective multiparticulate systems capable of enhancing drug stability, bioavailability, and controlled release properties. Aspirin (acetylsalicylic acid), a commonly used non-steroidal anti-inflammatory drug (NSAID), exhibits analgesic, antipyretic, anti-inflammatory, and antiplatelet activities. However, conventional aspirin therapy is often associated with adverse gastrointestinal effects and rapid systemic clearance, necessitating frequent dosing. These limitations highlight the need for controlled-release formulations that can maintain steady therapeutic levels and minimize side effects.

The coacervation phase separation method is widely used in microencapsulation due to its ability to yield uniform and stable microspheres with high entrapment efficiency. Polymers such as gelatin and carbopol are particularly suitable for microsphere formation because of their biocompatibility, gel-forming ability, and matrix-modifying characteristics. In this study, aspirin microspheres were formulated using gelatin and gelatin–carbopol combinations in different ratios to identify an optimized formulation that offers sustained drug release and acceptable physicochemical characteristics.

Comprehensive evaluation of the microspheres included particle size analysis, flow properties, in-vitro drug release, drug entrapment efficiency, IR spectroscopic compatibility, and assay using HPLC. The findings from this research provide insight into the potential application

of coacervation-based microspheres in delivering aspirin in a controlled-release manner, potentially improving therapeutic efficacy and patient compliance.

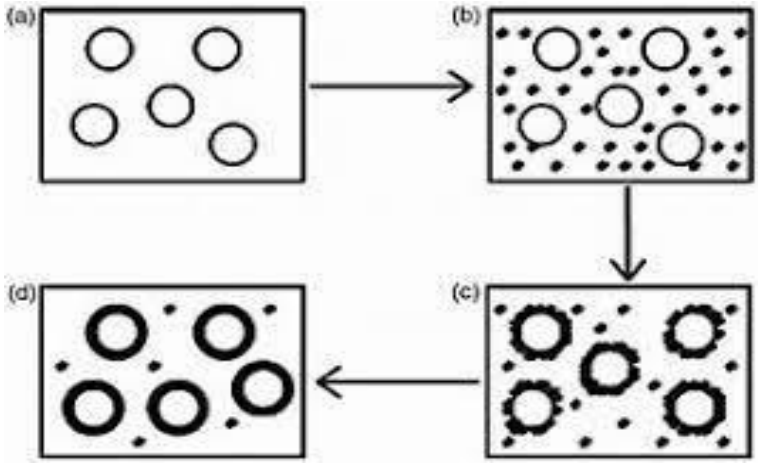

Fig. 1: Coacervation Phase Separation Method.

a) Core material dispersed in solution of polymer.
b) Separation of coacervate from solution.
c) Coating of core material by coacervate.
d) coalescence of coacervate to form uniform shell.

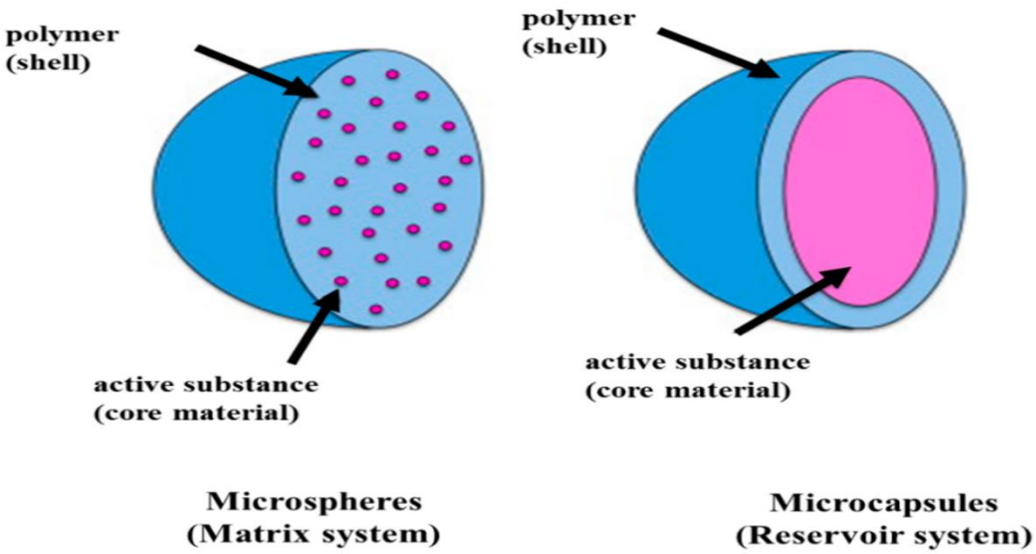

Fig. 2: Microencapsulation.

2. DRUG PROFILE

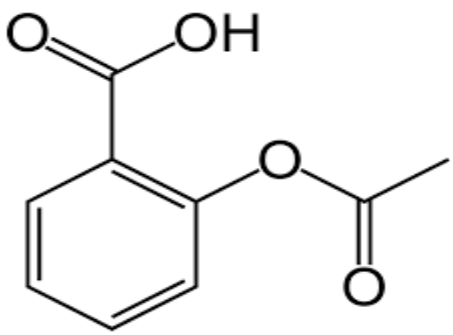

Fig. 3: Structure Of Aspirin.

2.1 SYSTEMATIC (IUPAC) NAME
- 2-Acetoxybenzoic acid

2.2 PHARMACOKINETIC DATA
- **Bioavailability:** Rapidly and completely absorbed
- **Protein Binding:** 99.60%
- **Metabolism :** Hepatic

2.3 HALF-LIFE
- **300-650 mg Dose :** 3.1 -3.2 hours
- **1 g Dose :** 5 hours
- **2 g Dose :** 9 hours

2.4 EXCRETION
- Renal

2.5 SYNONYMS
- 2-acetyloxybenzoic acid
- Acetylsalicylate
- Acetylsalicylic acid
- O-acetylsalicylic acid

2.6 CHEMICAL DATA
- **Formula:** $C_9H_8O_4$
- **Mol. Mass:** 180.157 g/mol

2.7 PHYSICAL DATA
- **Density:** 1.40g/cm^3
- **Melting Point:** 135 ^{O}C (275 ^{O}F)
- **Boiling Point:** 140^{o}c (284^{o}F) (decomposes)
- **Solubility In Water:** 3 mg/ml (20^{o} C)

2.8 CATEGORY
- Platelet aggregation inhibitors, Non-steroidal anti-inflammatory drug.

2.9 ACTION

Aspirin is an analgesic, anti-inflammatory and anti-pyretic. It inhibits cyclooxygenase, which is responsible for the synthesis of prostaglandin and thromboxane. It also inhibits platelet aggregation.

2.10 DURATION
- 4 to 6 hours

2.11 INDICATION AND DOSAGE
- Oral 50 mg,75 mg,100 mg,300 mg

2.12 CONTRA-INDICATION
- Hypersensitivity (attacks of asthma angioedema, urticarial or rhnities); active peptic ulceration; pregnancy (3rd trimester), children<12 yrs; patients with haemophilia or haemorrhagic disorders; gout; severe renal or hepatic impairment; lactation.

2.13 SPECIAL POPULATIONS
- History of peptic ulcer or these prone or dyspepsia and these with gastric mucosalesion; asthma or allergic disorders; dehydrated patients; uncontrolled hypertension; impaired renal or hepatic function; elderly.

2.14 INTERACTION
- Many potentiate effects of anticoagulants, methotrexate and oral hypoglycemics

2.15 ADVERSE DRUG REACTION
- GI disturbances; prolonged bleeding time, rhinitis, urtricaria and epigastric discomfort, angio edema, salicylism, tinnitus, broncho spasm.

2.16 LAB INTERACTION
- Interferably with thyroid function tests

2.17 INTERACTION WITH FOOD
- Preferably given on full stomach, vitamin-rich foods increase urinary excretion.

3. MATERIALS AND METHODS

3.1 METHOD OF PREPARATION

Table No. 1: Formulation Table.

S.NO	INGREDIENTS	F1	F2	F3	F4	F5	F6
1.	ASPIRIN	75 mg	75 mg	75 mg	75 mg	75 mg	75 mg
2.	GELATIN	50 mg	37.5 mg	2.5 mg	100 mg	75 mg	50 mg
3.	CARBAPOL	25 mg	37.5 mg	50 mg	50 mg	75 mg	100 mg
4.	GLUTARALDEHYDE	2 ml	2 ml	2 ml	2 ml	2 ml	2 ml
5.	LIQUID PARAFFIN	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S

Gelatin and gelatin-carbopol mixture containing Aspirin micro spheres were prepared by coaceravtion phase separation technique utilizing temperature change. Gelatin was dissolved in 10ml of water which was previously heated to 50^{o}c, to this aspirin was added and stirred approximately at 300 rpm with the help of magnetic stirrer for 15 mins to get a stable dispersion .The dispersion was poured drop wise into the 10ml of sunflower oil which was also previously heated to 50^{o}c on a water bath.

The mixture was stirred with a help of magnetic stirrer for 2 hrs at 300 rpm at room temperature. At the end of 2 hrs cross linking agent such as formaldehyde 0.5 ml was added to the dispersion medium and stirring was continued for next 30 mins. Finally it was kept in refrigerator for 24 hrs to ensure the rigidization of micro spheres, This procedure was followed to prepare 3 batches of Aspirin micro spheres with different ratios of gelatin and gelatin-carbopol mixtures.

3.2 IN-VITRO RELEASE STUDIES

The in-vitro dissolution test was carried out in the USP apparatus type 1, 900ml of dissolution medium containing mixed phosphate buffer P^H 6.8 previously held at 36.5° to 37.5° was taken and rotate the basket at 100 revolutions per minute. Every 15 minutes, withdraw a sample of the medium and filter. Immediately measure the absorbance of the filtrate, at 265 nm. Calculate the total content of aspirin.

3.3 DETERMINATION OF DRUG ENTRAPMET

An aliquot of 100 mg of micro spheres was triturated with distilled water. The volume was made up to 100 ml with distilled water and was sonicated for 2 hrs. It was then filtered to remove debris and the absorbance was measured by using Shimadzu UV/Vis spectrophotometer (UV-1601) at 265 mm. Quantitative estimation of Aspirin was calculated by using equation obtained by linear regression analysis of the calibration of aspirin in distilled water.

% Entrapment = Actual content/Theoretical content x 100

3.4 ASSAY

Mobile phase: Dissolve 2 gm of sodium 1-heptanesulfonate in a mixture of 850 ml of water and 150 ml of acetonitrile and adjust with glacial acetic acid to a P^H of 3.4.

- **Diluting solution :** prepare a mixture of acetonitrile and formic acid (99:1)
- **Standard Preparation :**Dissolve an accurately weighed quantity of aspirin in diluting solution to obtain a solution having a known concentration of about 0.5 mg per ml
- **Sample Preparation:** Weigh and finely powder. Transfer an accurately weighed quantity of the powder equivalent to about 100 mg of aspirin to a suitable container. Add 20 ml of diluting solution. shake vigorously (stock solution). Quantitatively dilute an accurately measured volume of stock solution with 9 volumes of diluting solution (assay preparation).

Procedure: Separately inject equal volumes (10µl) of standard preparation and sample solution, record the chromatograms and measure the responses for the major peaks. The chromatographic conditions are as follows.

- **Column:** 4.0 mm x 300 mm (C18)
- **Flow rate:** About 2.0 ml / min
- **Detector:** Ultra violet , Wavelength set at 280 mm
- **Injection volume:** 20 micro liters
- **Mobile phase:** acetonitrile (99) and formic acid (01)

Calculate Assay Contents As Follows

Sample avg. area x STD wt (in mgs) x 5 x50 x 50 x average Wt / STD avg. area x 50 x 50 x spl.wt (in mgs) x 5.

4. RESULTS AND DISCUSSIONS

4.1 PARTICLE SIZE ANALYSIS

Table No. 2: Shows Particle Size Analysis Data Of F_1.

S.NO	SIEVE NO.	SIEVE SIZE (mm)	WEIGHT OF POWDER DETAINED	% OF WEIGHT RETAINED
1.	8	2.0	0.2gms	0.40 %
2.	10	1.7	0.550gms	1.10%
3.	12	1.4	5.82gms	11.64%
4.	18	0.850	43.15gms	86.30%
5.	22	0.710	0.28gms	0.56%

Table No. 3: Shows Particle Size Analysis Data Of F_2.

S.NO	SIEVE NO.	SIEVE SIZE (mm)	WEIGHT OF POWDER DETAINED	% OF WEIGHT RETAINED
1.	8	2.0	0 gms	0 %
2.	10	1.7	0.240gms	0.48%
3.	12	1.4	1.32gms	2.64%
4.	18	0.850	48.11gms	96.22%
5.	22	0.710	0.48gms	0.96%

Table No. 4: Shows Particle Size Analysis Data Of F_3.

S.NO	SIEVE NO.	SIEVE SIZE (mm)	WEIGHT OF POWDER DETAINED	% OF WEIGHT RETAINED
1.	8	2.0	1.32gms	2.64 %
2.	10	1.7	3.240gms	6.48%
3.	12	1.4	4.32gms	8.64%

4.	18	0.850	40.60gms	81.24%
5.	22	0.710	0.40gms	0.80%

Table No. 5: Shows Particle Size Analysis Data Of F_4.

S.NO	SIEVE NO.	SIEVE SIZE (mm)	WEIGHT OF POWDER DETAINED	% OF WEIGHT RETAINED
1.	8	2.0	0.24gms	0.4 %
2.	10	1.7	0.60gms	1.20 %
3.	12	1.4	5.94gms	11.98 %
4.	18	0.850	43.75gms	87.12 %
5.	22	0.710	0.78gms	0.76 %

Table No. 6: Shows Particle Size Analysis Data Of F_5.

S.NO	SIEVE NO.	SIEVE SIZE (mm)	WEIGHT OF POWDER DETAINED	% OF WEIGHT RETAINED
1.	8	2.0	0.32gms	0.51 %
2.	10	1.7	0.750gms	3.0 %
3.	12	1.4	6.26gms	12.24 %
4.	18	0.850	44.15gms	87.30 %
5.	22	0.710	0.43gms	0.46 %

Table No. 7: Shows Particle Size Analysis Data Of F_6.

S.NO	SIEVE NO.	SIEVE SIZE (mm)	WEIGHT OF POWDER DETAINED	% OF WEIGHT RETAINED
1.	8	2.0	0.46gms	0.70 %
2.	10	1.7	0.580gms	1.40 %
3.	12	1.4	6.38gms	12.44 %
4.	18	0.850	44.58gms	87.80 %
5.	22	0.710	0.60gms	0.66 %

4.2 STANDARD CALIBRATION CURVE

Table No: 8: Shows Standard Calibration Curve For Aspirin.

S.NO	CONCENTRATION	ABSORBANCE
1.	20	0.071
2.	40	0.138
3.	60	0.205
4.	80	0.281
5.	100	0.342

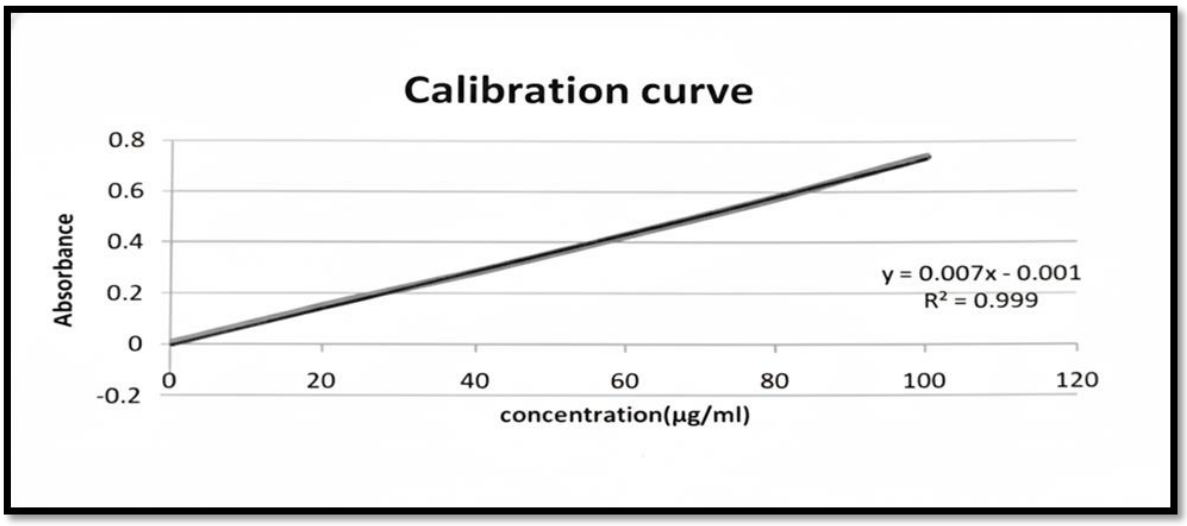

Fig: 4 Shows Aspirin Standard Calibration Curve.

Series of dilutions are made from standard working solution with 6.8P^{H} phosphate buffer to get concentration ranges from 20-100 µg/ml and the absorbance was measured at 265 nm and values are listed in table and calibration curve was drawn as shown in Fig. No :4

4.3 PRE-COMPRESSION OF PARAMETER

Table No. 9: Shows Pre-Compression Of Parameter.

S.NO	FORMULATION	BULK DENSITY	TAPPED DENSITY	HAUSNERS RATIO	CARR's INDEX	ANGLE OF REPOSE
1.	F1	1.16	1.44	1.241	19.5	38^{O} 22'
2.	F2	1.12	1.40	1.250	20	37^{O} 40'
3.	F3	1.24	1.20	1.081	7.5	36^{O} 34'
4.	F4	1.28	1.52	1.200	15.8	37^{O} 82'
5.	F5	1.26	1.60	1.270	21.25	37^{O} 51'
6.	F6	1.32	1.64	1.242	19.5	38^{O} 26'

4.4 DISSOLUTION TEST

Table No. 10: Shows Dissolution Parameters.

S.NO	FORMULATION	AT 0.5 HRS	AT 1.0 HRS	AT 1.5 HRS	AT 2 HRS	AT 2.5 HRS
1.	F1	16.00%	34.5%	49.65%	72.65%	93.8%
2.	F2	17.62%	36.54%	48.00%	69.84%	94.20%
3.	F3	16.85%	35.40%	50.15%	73.00%	96.92%
4.	F4	15.00%	33.45%	48.00%	71.05%	92.80%
5.	F5	14.86%	28.92%	44.00%	68.69%	89.10%
6.	F6	13.25%	27.40%	43.05%	65.00%	84.84%

4.5 HPLC ANALYSIS

Table No. 11: Shows Assay.

S.NO	FORMULATION	ASSAY	ENTRAPMENT VALUE
1.	F1	96.42 mg	96.42
2.	F2	97.85 mg	97.85
3.	F3	98.50 mg	98.50
4.	F4	97.15 mg	97.15
5.	F5	96.74 mg	96.74
6.	F6	96.50 mg	96.50

4.6 IR SPECTRUM

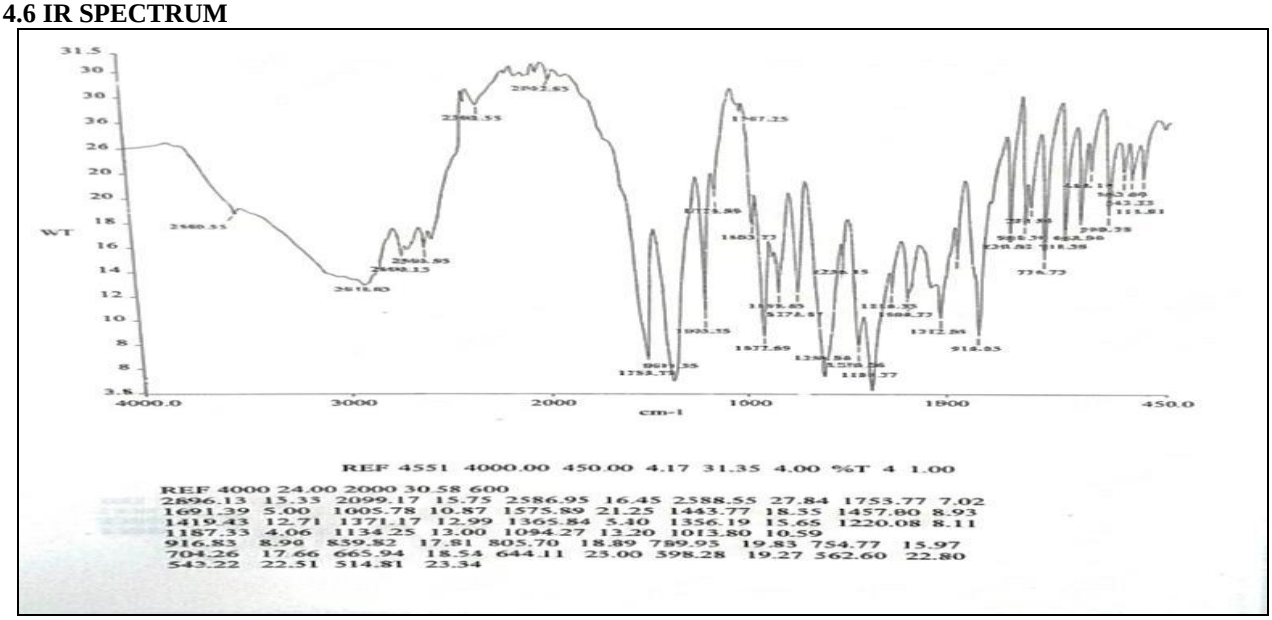

Fig No. 5: IR Aspirin Pure.

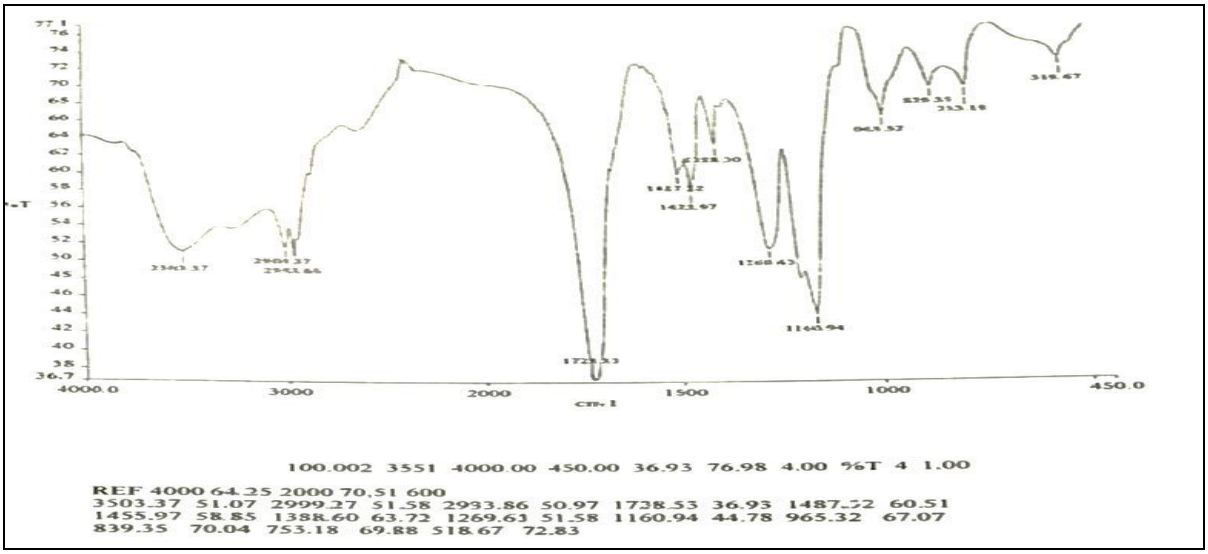

Fig No. 6: IR Carbopol.

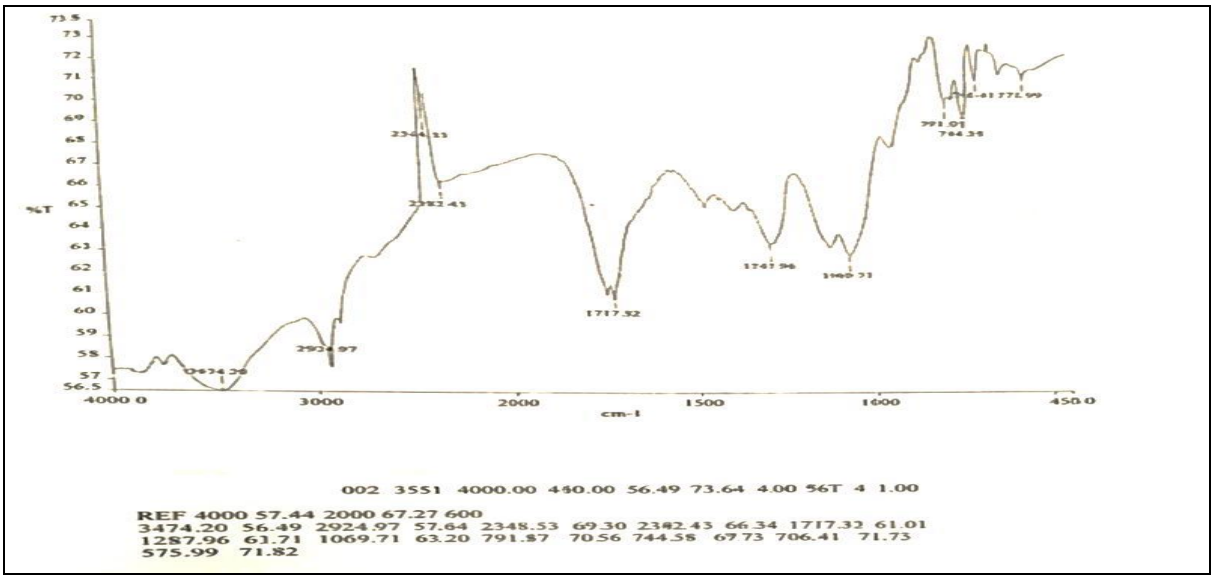

Fig No. 7: IR Gelatin.

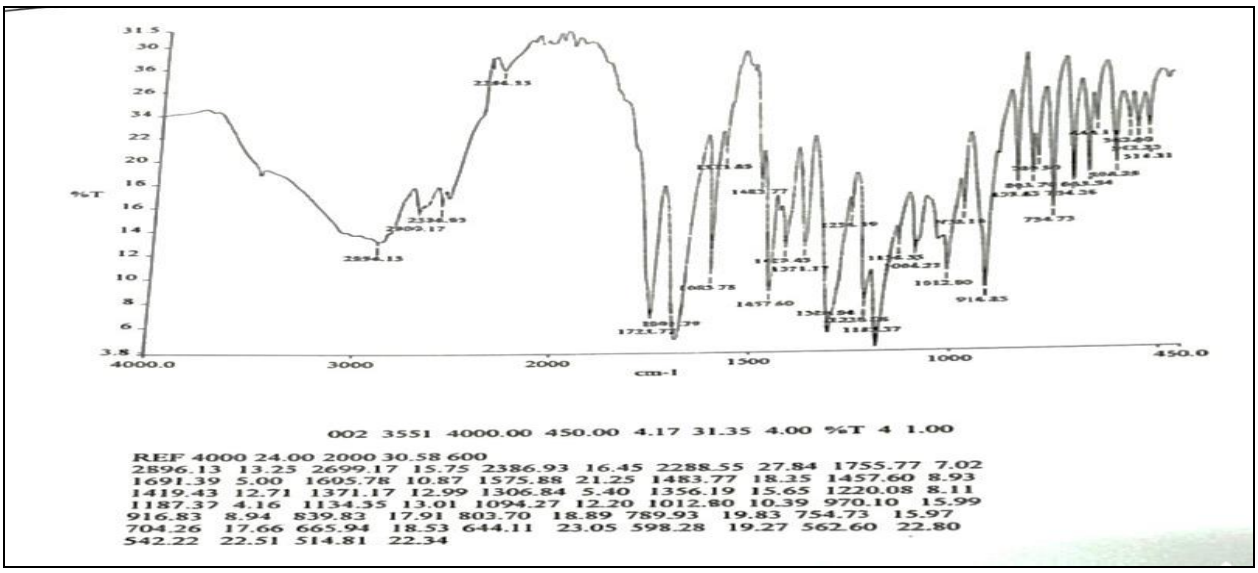

Fig No: 8 IR Microspheres (Aspirin With Polymer).

DISCUSSION

In the present work aspirin was formulated as Micro sphere which significantly increases the absorption and the drug release was maintained to therapeutic window of Aspirin. Before going to the formulation a detail literature review was carried out to know about the properties of drug, excipient, polymers and the methods adapted for preparation` Aspirin microsphere trial batches F_1 to F_6 were formulated using Aspirin and polymer (Gelatin & Carbopol) in different ratios. The different ratios were used to optimize the formulation. The particle size analysis was performed by sieving method. The maximum of particle size of micro sphere was around 850 µmin the three formulations. The bulk density values less than 1.2 gm /cm^3indicate good flow and values greater than 1.5 gm / cm^3indicate poor flow characteristic. The bulk density values are between 1.20 - 1.36 gm / cm^3.

Angle of repose was found to be less than or equal to 40^o indicates free flowing properties of the microcapsules. The angle of repose for all the formulations (F_1 to F_6) is seen to be between and indicating good flow property. The values of tapped density, carr's index, hausners ratio evaluated were found to be within prescribed limits and indicate good free flowing property. All the values show fair and good flow properties.

IR Spectrums shows there is no interactions between the aspirin and polymers. Among the all formulations, the formulation F3 was found to be promising because it shows better values than other formulations.

5. CONCLUSION

The present work was carried out to formulate the microspheres of Aspirin by coacervation phase separation technique. The evaluation study has been carried out for the Aspirin microspheres. The result shows that the microspheres have good flow properties and within limits. The prepared formulation have been evaluated for bulk density, carr's index, angle of repose, particle size analysis and found everything is within the IP limits. The Drug-polymer studies by IR Spectrum Evaluation shows the no interactions. The Release profile of Aspirin Microspheres shows the better Release profile The Assay of Aspirin by HPLC Method shows the satisfactory Aspirin content in the Microspheres, Hence the formulation can be chosen for further studies.

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