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DEVELOPMENT AND *IN-VITRO* CHARACTERIZATION OF SUSTAINED FLOATING HOLLOW MICROSPHERES CONTAINING LABETALOL HCL FOR THE TREATMENT OF HYPERTENSION

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Keywords:

Floating hollow microspheres, Solvent evaporation techniques, Gastro retentive drug delivery system (GRDDS), Labetalol HCl

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ABSTRACT: Aim: The present work for the development and *in-vitro* evaluation of sustained floating hollow microspheres (SFHM). **Materials and methods:** Sustained floating hollow microspheres were prepared by means of HPMC K4M, ethylcellulose and sodium alginate in various concentrations by using the solvent evaporation method using dichloromethane as solvent. The floating hollow microspheres of Labetalol HCl were formulated by the solvent evaporation method. SFHM was characterized using surface morphology by scanning electron microscopy (SEM), buoyancy studies, *in-vitro* floating behavior, incorporation efficiency, drug loading, production yield *in-vitro* drug release, and drug release kinetics studies. **Results:** The mean particle size ranges from 74.36± 1.02 to 102.0 ± 2.87µm. The entrapment efficiency of the drug ranges between 74.23 ± 2.12 to 80.82 ± 2.23%. The drug loading varies between 105.8 ± 1.46 to 125.2 ± 1.36µg/mg. The prepared hollow microspheres are exhibit good flowability. The *in-vitro* studies show release up to 12 h. The release kinetics data showed the best fit to the non-fickian release (diffusion and swelling). **Conclusion:** The outcomes conclude that Labetalol HCl SFHM may represent to expected option for greater bioavailability and improve patient consistency.

INTRODUCTION: Drugs that might be easily held from the gastrointestinal tract and having a short half-life are cleared out quickly from the systemic circulation. To short these complications, oral controlled drug delivery dosages were preferred. They convey the drug slowed into the GIT and keep up a reliable medicine center in the serum for a more drawn-out time period. Attempt's to improve oral medicine bioavailability have been created about the pharmaceutical business.

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As the number and concoction, arranged assortment of prescriptions has extended, new strategies are needed to develop orally dynamic therapeutics. In this way, GRDDS, which improves the prolongation of the drug in the GIT and improve their bioavailability, has been developed [1].

One of the most potent approaches for achieving a prolonged and obvious medicine transport profile in the GI package is to control the GRDFs.

Increased blood pressure is related to a linear increase in the endanger of CV disease. Starting with BP of 115/75 mm Hg, every 20mmHg increase in SBP and/or every 10mmHg increase in DBP doubles the chance of demise due to stroke, coronary heart ailment, or different vascular diseases Disease [2].

Elevated Systolic Blood Pressure has the strongest link with cardiovascular disease, although other blood pressure components are also associated with cardiovascular disease, including diastolic blood pressure, blood pressure variability, and mean arterial blood pressure [3].

Labetalol HCl is a mixed β- blocker. It ties seriously with each alpha and β-receptors. It is somewhat solvent in water and may be very much assimilated from the GI lot. LHCL is quickly assimilated following an oral component but studies wide first-pass metabolism, bringing approximately simply 25% oral bioavailability. The drug is disposed of quickly, so rehashing daily organization is needed to maintain viable plasma levels. The half-existence of LHCL is roughly 4–6 hrs. It has a lower molecular mass (364.9) and positive log P that value is 1.89.

The point of the present work was to develop and *in-vitro* evaluate sustained release floating Hallow microspheres of Labetalol hydrochloride. Floating hollow microspheres of Labetalol Hydrochloride for enhancing the drug bioavailability by prolongation of GRT. Solubility of the Labetalol HCl decreases with an increase in pH, making the stomach a better site of absorption. Hence an attempt has been made to formulate a GI floating hollow microsphere of the selected drug. Floating hollow microspheres help in retaining the hollow microspheres in stomach fluids for a longer duration and better absorption with site-specificity.

MATERIALS AND METHODS: Labetalol HCl was gift sample from the Aurobindo Pharma Pvt. Ltd., Sodium alginate bought from Sd. fine chemicals, Mumbai, HPMC K4M, is purchased from the Otto Chem. Laboratories Pvt. Ltd., Ethylcellulose is purchased from Loba Chemicals Pvt. Ltd., other chemical compounds have been analytical grade.

Preparation of Labetalol HCl Hollow Microspheres: [4] Hollow microspheres have been prepared by solvent evaporation techniques. Labetalol HCl, HPMC K4M, and EC and HPMC K4M, and Sodium alginate at various concentrations have been dissolved in a blend of ethanol and dichloromethane at room temperature. These were crammed 250mL of water containing 0.01% Tween 80 kept up at a temperature of 30–40°C and therefore stirred at ranging agitation pace to permit the volatile solvent to evaporate. The prepared hollow microspheres have been filtered, washed with distilled water, at 40°C hollow microspheres were dried.

TABLE 1: FORMULA FOR LABETALOL HCl FLOATING HALLOW MICROSPHERES USING DIFFERENT POLYMER BLENDS RATIOS AT DIFFERENT PROCESS PARAMETERS

Formula	Drug	Polymer type	Polymer blend ratio	Stirring rate (rpm)	Solvent ratio (ethanol + dichloromethane)
F1	200 mg	HPMCK4M: EC	1.:4	1000	1:1
F2	200 mg	HPMCK4M: EC	2:3	1000	1:1
F3	200 mg	HPMCK4M: EC	2.5:2.5	1000	1:1
F4	200 mg	HPMCK4M: EC	3:2	1000	1:1
F5	200 mg	HPMCK4M: EC	4:1	1000	1:1
F6	200 mg	HPMCK4M: SA	1.:4	1000	1:1
F7	200 mg	HPMCK4M: SA	2:3	1000	1:1
F8	200 mg	HPMCK4M: SA	2.5:2.5	1000	1:1
F9	200 mg	HPMCK4M: SA	3:2	1000	1:1
F10	200 mg	HPMCK4M: SA	4:1	1000	1:1

Structural Characterization of Labetalol HCl Hollow Microspheres:

Evaluation of Compatibility of Drug with Polymer by using FTIR Spectroscopy: [5] Drug-polymer compatibilities were examined using FTIR spectroscopy. Spectral values have been recorded for the drug, drug with ethylcellulose, a drug with sodium alginate, a drug with HPMCK4M, and drug with all polymer mixture. 3mg of drug was mixed with 100mg of KBr (dried at 40-50°C). The blend was taken and compressed under 10-ton pressure in a hydraulic press to form a transparent pellet. The same experiment is followed for all remaining excipients used. The sample has been examined at a resolution of 1 cm^{-1} and scanned between 4000 to 400 cm^{-1}.

Differential Scanning Calorimetry (DSC): [5] DSC thermograms of Labetalol HCl and drug with polymers were examined by using differential

scanning calorimetry to estimate possible interaction between drug-polymer. The samples have been placed in a flat-bottomed aluminum pan and maintain the constant heat (10°C/min) under nitrogen purge at a flow rate of 25ml/min. The data collection was conducted at a temperature range of 30-400°C.

Characterization of Preformulation Parameter:

Angle of Repose: [6] The flowability of floating hollow microspheres is usually examined by determining the angle of repose. Using fixed funnel method is used to determine the angle of repose. The hollow microspheres could fall freely through a funnel until apex of the conical pile just touched the tip of the funnel. The following formula was used to determine the angle of repose (ø).

Angler of repose $\Theta = Tan^{-1}$/ Height of the pile (h)/ radius of the base of the pile formed by the flooting microballoons (r)

Bulk Density / Fluff Density: [7, 8] In this study hollow microspheres were transferred to a measuring cylinder and the volume was recorded.

This volume is bulk volume and it includes true volume of the powder and the void space amongst hollow microspheres.

Bulk density (Db) = Mass of the (M)/ Nulk volume of the micriballoons (Vb)

Tapped Density: [9, 10] Tapped density of hollow microspheres was done by the tapping method. Formulated hollow microspheres (2g) were transferred into 10 mL measuring cylinder.

After noted hallow microspheres initial volume, the tapping was continued on a wooden surface until no further change in volume was calculated using tapped density equipment (Pharma Chem Machineries, model C-BD 100). The following formula was to calculate the tapped density.

Tapped density = mass of hallow microspheres in grams/ Volume of hallow microspheres after tapping in $cm^3 \times 100$

Carr's Compressibility Index: [11, 12, 13] Carr's Compressibility index is calculated using the following formula.

$$CI = Dt - Db/Dt \times 100$$

Where, Dt is the tapped density, Db is the bulk density.

Hausner's Ratio: [11, 12, 13] It is an index of ease for powder flow. It is calculated by the following formula.

Hausner s ration = Dt/Db

Where, Dt is the tapped density, Db is the bulk density.

Characterization of Hollow Microspheres:

Particle Size: [5, 14] The particle size determination of hollow microspheres was resolved with an optical microscopic technique using polarized light and calibrated ocular micrometer was to measure the mean particle size.

Surface Morphology by SEM: [15, 16, 17, 18] SEM of drug incorporated floating hollow microspheres were taken by coating the dried hollow Microspheres with gold (100 A°) under an argon atmosphere in a gold coating and was placed in the SEM chamber.

A scanning electron microscopy was taken at the acceleration voltage of 20 KV. This shows the morphological characteristics of Labetalol HCl hollow Microspheres and scanning electron micrographs were observed.

Buoyancy Percentage: [19, 20] The Buoyancy test of the hallow microspheres was done utilizing USP II (paddle type) disintegration apparatus (DS 8000, LAB INDIA). Dissolution test solution simulated gastric liquid (SGF) containing Tween 80 (0.02% v/v) was used as a dispersion medium to simulate gastric liquid.

The hallow microspheres were spread over the surface of the dissolution test solution, pH 1.2 (900 mL, 37 ± 0.5°C), which was unsettled by a paddle rotated at 100 rpm for 12 h. After stirring for previously determined intervals, the hollow microspheres that have been floating and the ones the settled to the bottom of the flask were recovered separately. After drying, the fraction of the hollow microspheres were weighed. The percentage buoyancy of hollow microspheres was accompanied by the following equation.

% Buoyancy = weight floating hallow microspheres after drying/weight of floating + hallow microspheres after drying × 100

***In-vitro* Floating Ability:** [21] 50mg of floating hollow microspheres have been taken in a 50ml beaker. 20 ml of 0.1N HCl containing 0.02% tween 20 was added to that. The beaker was shaken horizontally in a water bath at 37+/-0.1^{o}C. Floated particles were gathered after 10 h and dried in a desiccator till constant weight.

This procedure was implemented to all of the batches. The percent of floating hollow microspheres was calculated using the following formula.

% Floating ability = Weight of floating microspheres/Initial weight of microspheres × 100

Entrapment Efficiency: [22] To assess the entrapment efficiency, hollow microspheres (30mg) have been properly triturated and suspended in a minimum amount of alcohol, that solution diluted with 0.1N HCl (pH1.2) and filtered to separate shell fragments, amount of Labetalol HCl was analyzed spectrophotometrically at 303nm.

In order to calculate the percentage yield, the prepared hollow microspheres were collected and weighed. The entrapment efficiency and yield were calculated using the following equations

% Entrapment efficiency = calculted drug concentration/Theoritical drug content

Drug loading = Mass of the in hallow microspheres/ Mass of the recovered hallow microspheres

Determination of % Yield of Hallow Micro-spheres: [22] The percent yield was calculated as the weight of hollow microspheres obtained from each batch divided by total weight of drug and excipient used to prepare that batch multiplied by 100.

% Yield = Mass of the hallow microspheres obtained/Total weight of excipient and drug × 100

***In-vitro* Drug Release Studies:** [23] The *in-vitro* drug delivery from hallow microspheres was determined utilizing USP II dissolution test equipment. The dissolution test was carried out using 0.1NHCl (pH 1.2) as dissolution medium (900 mL) kept up at 37 ± 0.5°C at 100 rpm. 5ml of sample withdrawn from the dissolution test apparatus. For 12 h and the sample was replaced with a new dissolution medium to keep the sink condition. Withdrawn samples were investigated using an ultraviolet spectrophotometer at 303 nm. All experiments have been carried out in triplicate.

Drug Release Kinetics: [11] Data collection from In vitro release study was inserted into various kinetic equations. The kinetic equations used were zero order (aggregate level of drug release versus time), first order (log cumulative percentage of drug remaining versus time), the Higuchi model (cumulative percentage of drug release versus square root of time), and Korsmeyer-Peppas (log cumulative percent drug release versus log of time). Relapse (r^2) values were calculated for linear curves obtained by regression analysis.

RESULTS AND DISCUSSION:

Identification and Incompatibility of Drug with Polymers by FTIR: The FTIR study was conducted out for pure drugs, polymers (Ethylcellulose, Sodium alginate, and HPMC K4M) and their physical mixtures. FTIR spectra are shown in **Fig. 1**.

The results of IR spectral analysis showed the following major peaks for Labetalol HCl, polymers (Ethylcellulose, sodium alginate, and HPMC K4M), and their physical blend which are tabulated in **Table 2**. The drug-polymer interactions were ruled out as there were no major shifts in absorption peaks of Labetalol HCl in the presence of polymer combinations *viz*. Ethylcellulose, Sodium alginate, and HPMC K4M.

TABLE 2: IR SPECTRAL PEAKS OF LABETALOL HCL AND POLYMERS

Drug/Polymer	O-H Stretch cm^{-1}	N-H Stretch cm^{-1}	C-H stretch cm^{-1}	C=O Stretch cm^{-1}	C-N stretch cm^{-1}	C=C bend cm^{-1}
L HCl	3915	3461	2977	1746	1316	823
LHCl + EC	3965	3453	2977	1745	1315	822
LHCl + SA	3920	3475	2977	1738	1316	823
LHCl + HPMC K4M	3942	3461	2977	1747	1314	812
LHCl + All polymer	3901	3461	2977	1747.08	1314	812.60

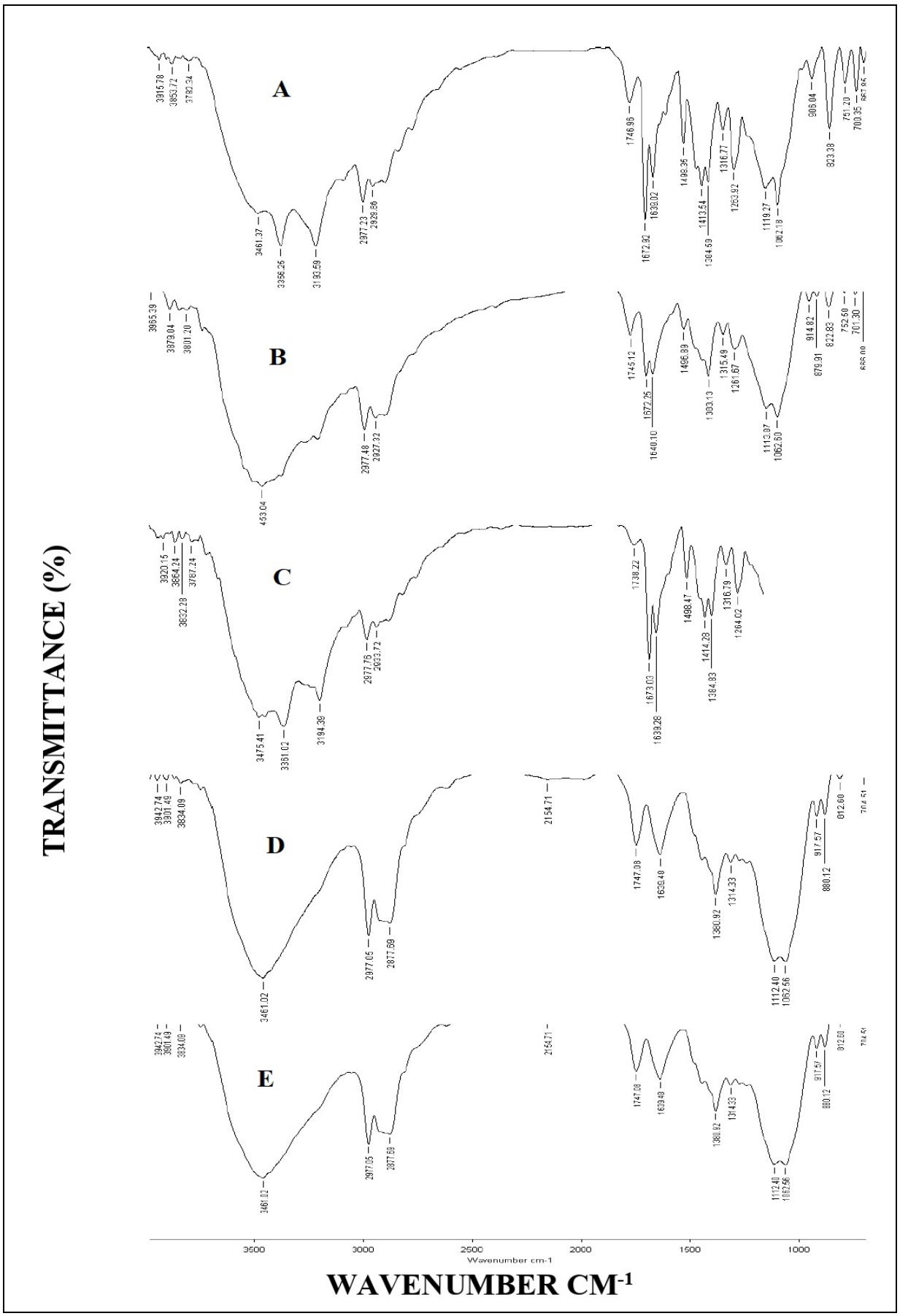

FIG. 1: FTIR SPECTRUM OF A) LABETALOL HCl B) L HCl WITH ETHYL CELLULOSE C) LHCl WITH SODIUM ALGINATE D) L HCl WITH HPMC K4M E) L HCl WITH ALL POLYMERS

Identification and Incompatibility of Drug with Polymers by DSC: DSC thermograms of pure drug, polymeric components, and mixtures are shown in **Fig. 2**. The DSC thermogram of Labetalol HCl exhibited an endothermic peak at 198°C, which was distinct from peaks observed in thermograms of the different polymeric components.

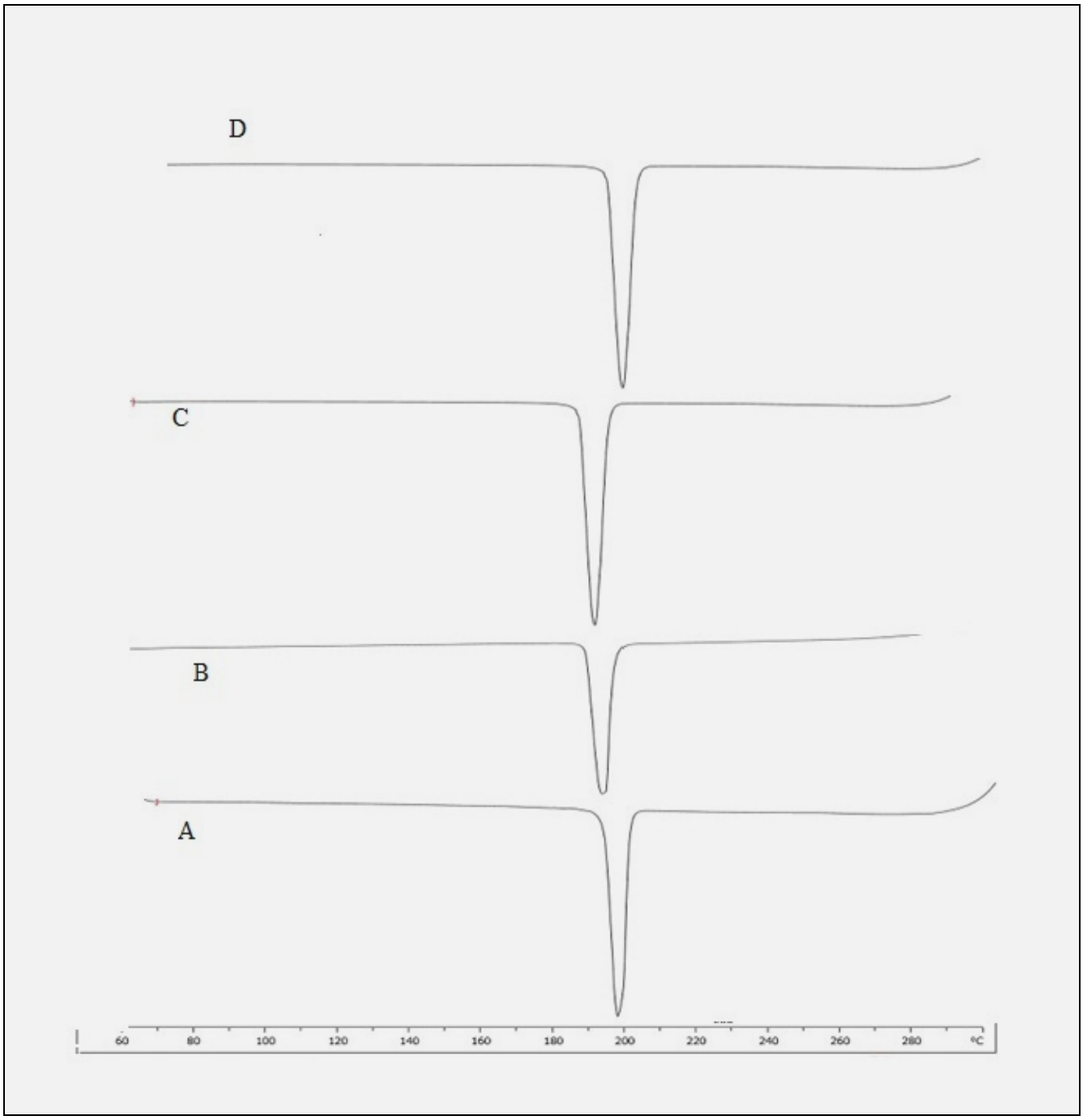

FIG. 2: DSC THERMOGRAMS OF A) LABETALOL HCL, B) LABETALOL HCL AND SODIUM ALGINATE C) LABETALOL HCL AND HPMCK4M D) MIXTURE

Evaluation Results of Preformulation Studies:

Micromeritic Studies: All the formulated batches of Labetalol HCl Hollow Microspheres shown good flow properties with a value of angle of repose between the range of 31°34'- 38°27'. The bulk density and tapped density of all formulations were within short range *i.e.* 0.07 ± 2.63 to 0.14 ± 2.01 gm/cm^3 and 0.08 ± 1.25 to 0.14 ± 1.52 gm/cm^3. Hausner's ratio was less than 1.10 for all formulations, which indicates better flow characteristics of microspheres and the results were mentioned in **Table 3**.

Evaluation Results of Prepared Labetalol HCl Hollow Microspheres:

Particle Size: Particle size analysis is various formulations of Labetalol HCl was carried out using a digital micrometer. By increasing the surfactant, the mean particle size of hollow microspheres increased. The mean particle size ranges from 74.36 ± 1.02 to 102.0 ± 2.87µm.

Surface Morphology by SEM: The SEM showed that the evolved floating Hallow microspheres were spherical with a porous surface which facilitate diffusion of the drug, as shown in **Fig. 3**.

Buoyancy Percentage: The prepared hallow microspheres evaluated the percentage buoyancy. The buoyancy percentage for all formulations was above 70%, which was studied for 12hrs. The highest percentage was acquired with formulation F7. Buoyancy percentage between from 73.60 ± 2.0 to 80.40 ± 2.0. The results were shown in **Table 4**.

***In-vitro* Floating Ability:** The prepared all formulations of Labetalol hollow microspheres are exhibit good floating ability. Such floating performance was because of the insolubility of polymers in the GI fluid. It was found that the floating ability increased with increasing average particle size. The floating ability of hollow microspheres is shown in **Fig. 4**.

Entrapment Efficiency: The drug entrapment efficiency of hollow microspheres was observed to be precise (74.23 ± 2.12 to 80.82 ± 2.23%). This may be due to the insolubility of drugs in water. The results have been shown in **Table 4**.

Determination of % Yield: The drug percentage yield of all formulations ranges from 72.23 ± 1.62 to 80.82 ± 2.23. As polymer concentration increases, the yield of hollow microspheres was also found to increase. The results were shown in **Table 4**.

***In-vitro* Drug Release Kinetics:** From the *in-vitro* dissolution observes of all formulations (F1-F10), formulation F7 releases around 90.12% of drug at the final of 12 hours for a sustained release. Therefore, the F7 formulation was chosen as the best formulation from all ten formulations. The results were shown in **Table 5** and **Fig. 5**.

Drug Release Kinetics: The regression coefficient values and n values show that the drug releases comply with Non - Fickian release (Diffusion and swelling). The results were shown in **Table 6.**

TABLE 3: BUOYANCY & MICROMETRIC PROPERTIES OF LABETALOL HCl FLOATING HOLLOW MICROSPHERES

Formulation Code	Bulk density gm/cc	Tapped density gm/cc	Hausner's ratio	Carr's index	Angle of Repose
F1	0.11 ± 2.01	0.13 ± 1.03	1.12 ± 2.11	10.2 ± 2.21	30°32' ± 1.01
F2	0.11 ± 1.70	0.12 ± 1.32	1.10 ± 1.26	9.22 ± 1.92	30°23' ± 1.11
F3	0.12 ± 1.88	0.11 ± 1.23	1.18 ± 1.32	14.5 ± 2.54	32°52' ± 1.08
F4	0.07 ± 2.63	0.12 ± 1.02	1.13 ± 1.02	11.4 ± 1.99	32°42' ± 1.11
F5	0.08 ± 1.19	0.11 ± 1.32	1.10 ± 1.28	12.5 ± 2.54	34°53' ± 1.92
F6	0.12 ± 2.04	0.13 ± 1.32	1.18 ± 1.22	12.4 ± 2.22	32°32' ± 1.88
F7	0.14 ± 2.01	0.12 ± 1.25	1.15 ± 1.26	14.5 ± 2.26	34°88' ± 1.76
F8	0.06 ± 1.62	0.14 ± 1.52	1.12 ± 2.55	12.2 ± 1.85	38°88' ± 1.23
F9	0.07 ± 1.88	0.08 ± 1.25	1.16 ± 1.02	9.23 ± 1.85	36°64' ± 1.90
F10	0.06 ± 2.24	0.09 ± 1.56	1.14 ± 1.28	11.4 ± 1.96	38°27' ± 1.80

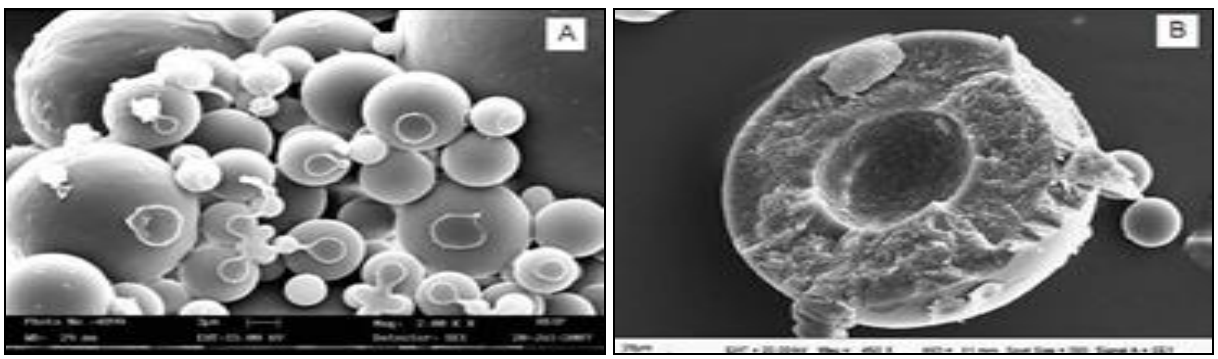

FIG. 3: SEM OF HALLOW MICROSPHERES: (A) OUTER SURFACE; (B) INTERNAL SURFACE OF A CROSS-SECTION

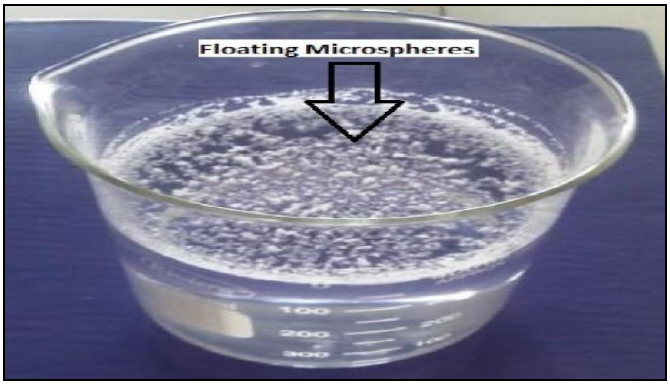

FIG. 4: FLOATING HOLLOW MICROSPHERES

TABLE 4: BUOYANCY PERCENTAGE, ENTRAPMENT EFFICIENCY, DRUG LOADING, PERCENTAGE YIELD OF LABETALOL HCL FLOATING HOLLOW MICROSPHERES

S. no.	Formulation code	Buoyancy (%)	Entrapment efficiency (%)	Drug loading	% yield
1	F1	73.60 ± 2.0	76.97 ± 1.55	116.0 ± 1.25	75.72 ± 1.54
2	F2	74.30 ± 2.0	80.25 ± 2.56	118.6 ± 1.62	78.23 ± 1.33
3	F3	76.60 ± 2.2	74.23 ± 2.12	116.6 ± 1.81	80.82 ± 2.23
4	F4	77.80. ± 1.8	76.97 ± 1.55	122.2 ± 1.65	76.97 ± 1.55
5	F5	74.60 ± 2.3	80.82 ± 2.23	114.2 ± 1.29	74.55 ± 2.62
6	F6	78.60 ± 2.8	78.23 ± 1.33	115.2 ±1.26	72.23 ± 1.62
7	F7	80.40 ± 2.0	80.72 ± 1.54	125.2 ± 1.36	75.23 ± 1.22
8	F8	76.30 ± 1.8	75.50 ± 1.82	114.3 ± 1.28	74.23 ± 2.12
9	F9	74.20 ± 2.1	76.36 ± 1.27	105.8 ± 1.46	80.25 ± 2.56
10	F10	76.60 ± 2.0	76.22 ± 1.32	111.9 ± 1.78	79.23 ± 1.85

TABLE 5: *IN-VITRO* RELEASE PROFILE

Time in h	Formulation code									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1	20.03±0.52	12.52±0.53	14.18±0.35	10.01±0.27	12.91±0.25	10.56±0.44	8.25±0.25	15.23±0.54	12.11±0.52	9.54±0.51
2	35.56±0.58	32.56±0.54	31.56±0.31	28.19±0.35	22.12±0.41	15.99±0.48	13.11±0.32	25.76±0.23	22.77±0.53	13.84±0.51
4	54.25±0.25	53.29±0.42	45.25±0.44	62.43±0.58	32.12±0.51	28.21±0.45	24.72±0.25	37.54±0.32	30.99±0.45	24.15±0.62
6	68.56±0.27	77.38±0.32	63.14±0.52	76.13±0.25	52.23±0.59	44.14±0.26	40.99±0.52	53.26±0.33	48.12±0.32	43.12±0.61
8	89.42±0.45	96.36±0.52	92.02±0.57	92.23±0.45	78.12±0.52	58.98±0.32	56.25±0.32	79.24±0.45	69.32±0.62	54.65±0.52
10					94.42±0.46	78.68±0.14	72.84±0.45	90.47±0.52	93.51±0.52	72.74±0.23
12						87.04±0.52	90.12±0.31			85.25±0.52

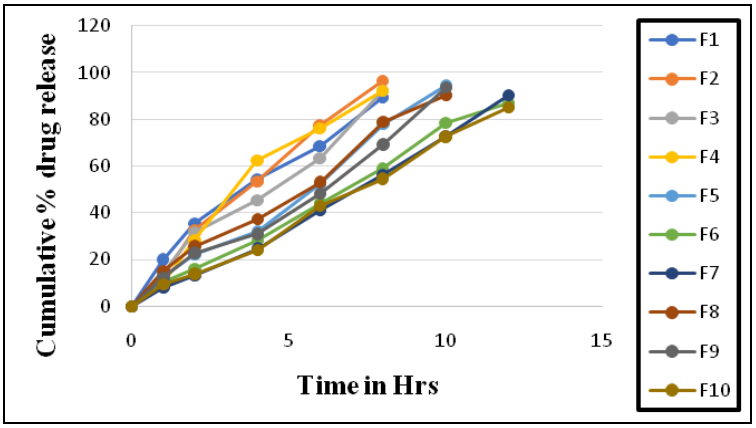

FIG. 5: *IN-VITRO* DISSOLUTION RELEASE PROFILE FOR F1 – F10 FORMULATIONS

TABLE 6: REGRESSION COEFFICIENT OF F7

Formulation	Regression coefficient (R^2) values			
	Zero order	First Order	Higuchi Model	Korsemeyer -peppas
Labetalol HCl floating hollow microspheres	0.9955	0.8278	0.8945	0.8400

n = 0.9735

CONCLUSION: The outcomes show that formulation F7 (drug and 1:4 ratio of HPMCK4M: Sodium alginate) of Labetalol HCl hollow microspheres so prepared will continue to be buoyant on the surface of GI fluid, releasing Labetalol HCl in sustained action. Inferences drawn from *in-vitro* studies suggest it has achieved the objective of considerable influence on physicochemical characteristics.

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CONFLICTS OF INTEREST: The authors declare that there is no conflict of interest.

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