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Research Article

Formulation and In-Vitro Characterization of Oral Controlled Release Microspheres of Itopride Hydrochloride

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A B S T R A C T

The aim of this work was to design a controlled release drug delivery system for the prokinetic agent Itopride Hydrochloride. Itopride Hydrochloride was encapsulate using ethyl cellulose and HPMC K 100 M by solvent evaporation method and physiochemical properties of formulation were characterized. The obtained microsphere showed good flow properties with angle of repose, bulk density, tapped density, Carr's index, Hausner'ratio was found to be 30⁰96'±0.45 to34⁰99'±0.12, 0.390±0.41g/ml to 0.423±0.55 g/ml, 0.438±0.23 g/ml to 0.484±0.88 g/ml, 10.72±0.43% to 15.25±0.38%,1.12±0.11 to 1.18±0.45 respectively. Using solvent evaporation method, microspheres percentage yield was found to be 78±0.77%-88.18±0.24%.The percentage entrapment efficiency of various formulations was found to be 80.72±0.99% to 91.72±0.12%. As concentration of polymer increases, it retards the release of drug upto 24 hours. As concentration of HPMC K100M increases drug release time increases. Optimized formulation E-9 contain 200 mg Itopride HCL, 450 mg of HPMC K 100M and 450 mg of Ethyl Cellulose. The result of formulation E-9 for Angle of Repose, Bulk Density, Tapped Density, Carr's Index, Hausners Ratio, Percent Yield, Drug Entrapment Efficiency, percent Cumulative Drug Release, Zeta Potential, Particle Size were 30⁰96'±0.45, 0.408±0.77, 0.457±0.23, 10.72±0.43, 1.12±0.1, 88.18±0.24%, 91.72±0.12%, 80.05±0.5%, 21.72mV, 747.7 µ respectively. It was concluded that the prepared controlled release microspheres of Itopride Hydrochloride may prove to be potential candidates for safe and effective controlled drug delivery.

Keywords: Microspheres, Controlled Release, Itopride Hydrochloride.

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INTRODUCTION

Itopride Hydrochloride is a prokinetic drug used gastro-esophageal reflux disease (GERD). Itopride Hydrochloride has anti- cholinesterase (AchE) activity as well as dopamine D2 receptor antagonistic activity and is being used for the symptomatic treatment of various gastrointestinal motility disorders. It has short half-life 6 h. Thus 50 mg thrice a day is required to maintain an effective plasma concentration. Such therapy leads to poor patient compliance. Therefore, slowrelease preparation seemed to be a logical approach in Itopride therapy [1,2,3]. One of the methods of controlled drug delivery system is by microencapsulation which is microspheres drug delivery system. So the aim of work was to prepare controlled release microspheres of itopride hydrochloride. Microspheres are small spherical particles, with diameters in the micrometer range (typically 1µm to 1000µm). Microspheres are defined as "Monolithic sphere or therapeutic agent distributed throughout the matrix either as a molecular dispersion of particles" (or) can be defined as structure made up of continuous phase of one or more miscible polymers in which drug particles are dispersed at the molecular or macroscopic level. Microspheres are sometimes referred to as micro particles.[4]

Oral modified-release multiple-unit dosage forms have always been more effective therapeutic alternative to conventional or immediate release single-unit dosage forms. With regards to the final dosage form, the multiparticulates are usually formulated into microspheres and filling them into hard gelatin capsules. Microspheres received much attention not only for prolonged release, but also for targeting of drugs.[4,5]

Microspheres have been prepared by solvent evaporation method, single emulsion method, hot melt micro encapsulation method, spray-drying ionic gelation and emulsion cross linking method of these methods, the most common method used to prepare microspheres is the solvent evaporation method. Solvent evaporation method is method in which dissolving drug and polymers in solvent and the resulting mixture was then added drop by drop into light liquid paraffin containing 1 % w/v Span 80 while stirring.[6]

MATERIAL S AND METHOD:

Materials:

Itopride Hydrochloride was obtained as a gift sample from Ami Life scieces Pvt. Ltd., Vadodara, Gujrat. HPMC K100 M was obtained as a gift sample from Colorcon Asia Pvt. Ltd., Goa. Ethyl Cellulose was procured from Loba Chemie Pvt. Ltd, Mumbai. Methanol, Dichloromethane, Liquid Paraffin, Span 80 were purchased from S.D. Fine Chemicals Ltd. Mumbai.

Method:

The microsphere was prepared by dissolving drug and polymers HPMC K 100 M and Ethyl Cellulose in methanol and dichloromethane (9:1). The resulting mixture was then added drop by drop into 100 ml light liquid paraffin previously containing 1 % w/v Span 80 while stirring continuously, stirring rate was 1000 RPM for 3 hrs until solvent was evaporated completely. The dispersed polymer was transferred into fine droplet, which subsequently solidified into rigid microsphere due to solvent evaporation. The particles were collected by filtration and washed 3 to 4 times with n-Hexane and then after microsphere dried at room temperature.[6]

Formulation Design:

Table 1: Formulation Design

Batch	Drug(mg)	HPMCK100M (mg)	Ethyl Cellulose (mg)
E1	200	150	150
E2	200	300	150
E3	200	450	150
E4	200	150	300
E5	200	300	300
E6	200	450	300
E7	200	150	450
E8	200	300	450
E9	200	450	450

MICROSPHERES CHARACTERIZATION:

Compatibility Study of Drug with Excipients:

Fourier Transform Infra-Red Spectroscopy[7]

The drug-excipients interaction was conducted using FTIR Spectrophotometer. Sample for the FTIR spectroscopy was prepared by mixing the samples with spectroscopy grade KBr and compressed into transparent pellets, then scanned in IR range from 500 to 4000 cm-^{1}FTIR spectra of drug and drug and polymer recorded using FTIR spectrophotometer.

Differential Scanning Calorimetry[8]

Differential Scanning Calorimetry studies were carried out using "Schimadzu DSC-60.7. In this study drug under gone thermal analysis. During the study, the temperature ranges from 40 to 300º C, heating rate 10 min and flow rate of nitrogen 10 ml/min were maintained. Approximately 2mg of samples were taken in Aluminum pan sealed and the thermogram was recorded.

Micromeritic Study[9-13]

Angle of Repose

Angle of Repose is the maximum angle between the surface of a pile of powder and horizontal plane. It is usually determined by Fixed Funnel Method and is the measure of the flowability of powder/granules.

$$\Theta = \tan^{-1}(h/r)$$

Where,

h=Height

r=radius

Θ =Angle of repose

Bulk Density

Bulk density is determined by measuring the volume of a known mass of a powder sample that has been passed through a screen into a graduated cylinder. The bulk volume of blend was determined. The bulk density calculated by using following formula,

$$\rho_b = m / V_b$$

Where,

ρ_b= Bulk density

m =mass of powder

Vb = initial/bulk volume

Tapped Density

Tapped Density is the volume of powder determine by tapping by using a measuring cylinder containing weight amount of sample. The measuring cylinder containing known mass of microsphere were tapped for fixed time, and minimum volume occupied in cylinder was determined.Tapped density was calculated by using following formula,

$$\rho_t = m/V_t$$

Where,

ρ_t= Tapped density

m= Mass of the powder

V_t=Final tapped Volume

Compressibility Index

The compressibility index is measures of the propensity of a powder to be compressed.

$$\% \text{ Compressibility} = \frac{\text{Tapped density- Bulk density}}{\text{Tapped density}} X100$$

Hausner Ratio

Flow property is very important parameter to be measured since it affects the mass of uniformity of the dose. It is usually predicted from Hausner Ratio and Angle of Repose Measurement.

Hausner Ratio = Tapped Density/Bulk Density

Percentage Yield[14,15]

The prepared microspheres of all batches were accurately weighed. The weight quantity of prepared microspheres was divided by the total amount of all the excipients and drug used in the preparation of the microspheres, which give the total percentage yield of microspheres. It was calculated by using following formula,

Percentage yield = Practical Yield/Theoretical YieldX100

Drug Entrapment Eficiency[16]

Entrapment efficiency of microspheres was evaluated by deriving percent drug entrapment. 10 mg of microspheres accurately weigh and crushed in glass mortar-pestle and then suspended in 10 ml of 6.8 Phosphate Buffer. After 24 hr the solution was filter through Whatman filter paper. The 1 ml of this filtrate is pipetted out and diluted upto the mark in 10 ml volumetric flask with Phosphate Buffer. Drug concentration was recorded by taking absorbance of this solution spectrophotometrically at 258 nm. The drug concentration was calculated. Thus, percent drug encapsulated in microsphere calculated by following formula,

$$\% \text{ drug entrapment} = \frac{\text{Calculated Drug Concentration}}{\text{Theoretical Drug Concentration}} x\ 100$$

In Vitro Dissolution Study[17]

The drug release rate from the microspheres was studied in a medium by changing pH using the USP dissolution test apparatus I at 37±0.5 °C with a rotation speed of 75 rpm. A weigh of amount of microspheres packed in capsule. Initially, the microspheres were treated with 900 mL of 0.1N hydrochloric acid (pH 1.2) for 2 hours. After 2 hours, 25.92 g disodium hydrogen phosphate and 10.305 g dihydrogen potassium phosphate were added to increase the pH to 6.8 and the drug release study was continued for another 24 hours. The samples were withdrawn at suitable intervals and replaced with fresh medium. The aliquots were suitably diluted and drug content was determined by UV.

Kinetics of drug release[18,19]

The invitro dissolution profile of all batches were fitted to Zero order, First order, Higuchi model, Korsemeyer Peppas model and Hixson Crowel Model to ascertain the kinetic modeling of drug release. Correlation coefficient (R2) values were calculated for linear curves obtained by the regression analysis of the above plot.

Zero-order kinetic model: Cumulative % drug released vs. time

First order kinetic model: log cumulative % drug remaining vs. t

Higuchi model: Cumulative % drug released vs. square root of t

Korsemeyer-Peppasmodel:Log cumulative % drug released vs. Log time

Hixson Crowel: Cubic Root of % Drug Remaining Vs t

Scanning Electron Microscopy (SEM)[16]

The surface morphology, size, shape of microspherewas determined by SEM. Dry microsphere were placed on electron microscope brass stub that was coated with gold (thickness 200 nm).in an ion sputter. The SEM images of microspheres taken at different magnifications.

Zeta potential[20]

The zeta potential is determined by using Malvern Zetasizer for optimized batch gives information on the charge of the particles and the tendency of the particles in a formulation to aggregate or to remain discrete.

Particle Size Analysis[21]

Particle size analysis can be done by using Malvern Zetasizer for optimized batch.

Stability Study[22,23]

Stability studies were carried out at 40°C±2°C/75%RH±5% for a specific period of up to 28 days for the optimized formulation.

RESULTS AND DISCUSSION:

Compatibility Study of Drug with Polymer:

Fourier-Transform Infrared Spectroscopy (FTIR) Study:

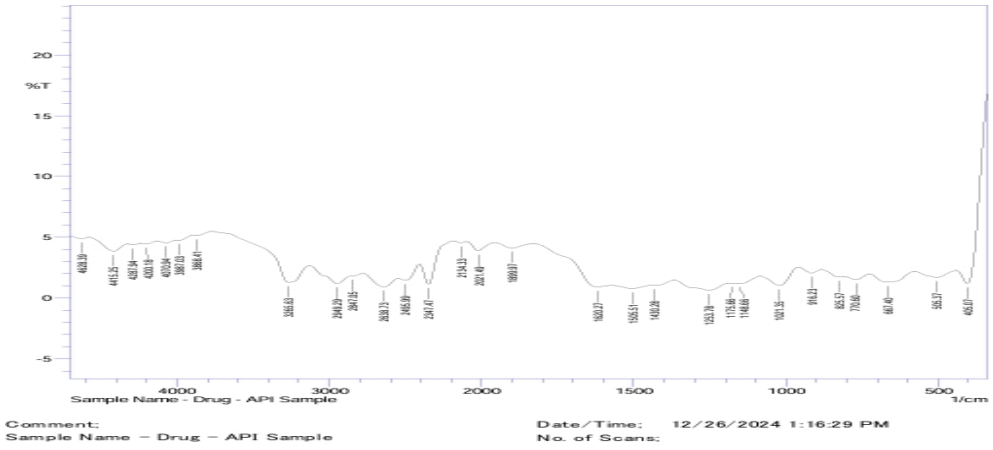

Figure 1: FTIR of Itopride HCL

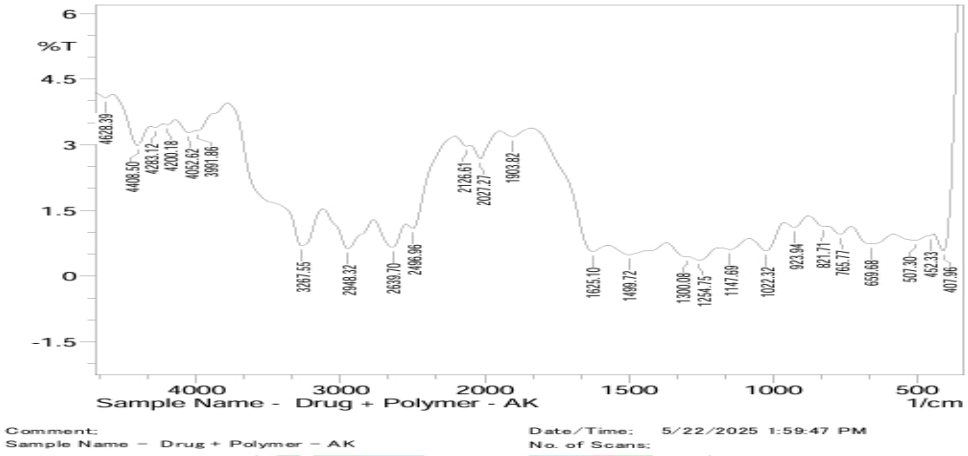

Figure 2: FTIR of Itopride HCL and Polymers Mixture

The FTIR spectra of Itopride HCl and the FTIR spectra of drug and polymer physical mixture shown in Figure No. 1 and 2 respectively.

The FTIR spectra of Itopride HCl depict characteristic absorption b and at 3265.63, 2949.29, 1620.27, 1430.28 and 1253.78cm−1 represent the presence of aromatic (NH) stretching vibrations, aliphatic C-H stretching, carbonyl (C=O) stretching, alkene (C=C) and C–O–C a symetric ether respectively. The FTIR spectra of drug and polymers physical mixturedepict characteristic absorption b and at 3267.55, 2948.32,1625.10,1499.72,1254.75 cm−1 represent the presence of aromatic (NH) stretching vibrations, aliphatic C-H stretching, carbonyl(C=O) stretching, alkene (C=C) and C–O –C a symetric ether respectively.

It was suggested that there is no interaction between drug and polymers.

Differential Scanning Calorimetry (DSC):

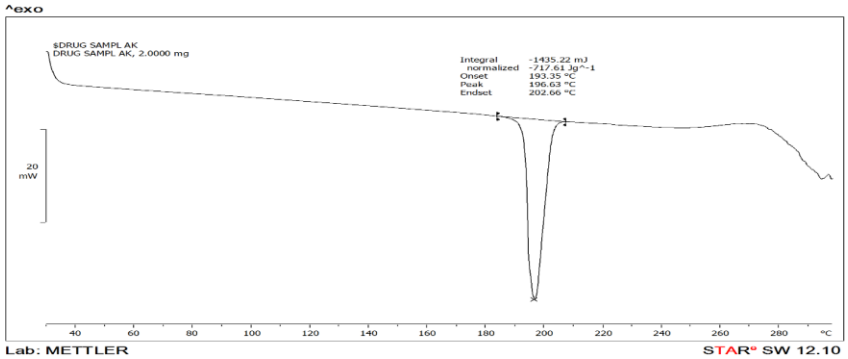

Figure 3: DSC Thermogram of Itopride Hydrochloride

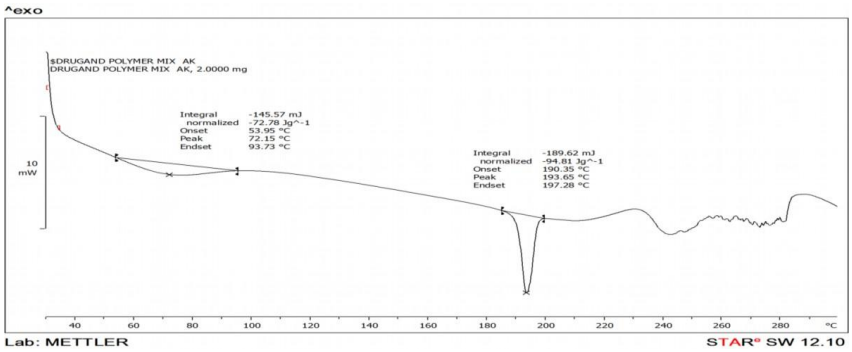

Figure 4: DSC Thermogram of Itopride Hydrochloride and Polymers

The DSC thermogram of Itopride Hydrochloride shows an endothermic peak at 196.63^{0}C and DSC thermogram of Itopride Hydrochloride and polymers shows an endothermic peak at 193.65^{0}C shown in Figure No. 3 and Figure No.4. No significant change in melting point of Itopride HCL with polymers. Physical mixture of Itopride with polymers showed presence of characteristics peaks of drug indicating physical compatibility between drug and polymers.

Micromeritics Study:

Table 2: Micromeritics Study of Microspheres

Batch	Angle of Repose	Bulk Density (g/ml)	Tapped Density (g/ml)	Carr's Index (%)	Huasner's Ratio
E1	34^{0}99'±0.12	0.400±0.76	0.472±0.99	15.25±0.38	1.18±0.45
E2	34^{0}38'±0.34	0.422±0.71	0.484±0.88	12.8±0.66	1.14±0.22
E3	33^{0}91'±0.67	0.403±0.11	0.458±0.89	12.08±0.53	1.13±0.57
E4	34^{0}21'±0.76	0.423±0.13	0.485±0.76	12.78±0.69	1.14±0.45
E5	32^{0}25'±0.77	0.390±0.65	0.442±0.65	11.76±0.45	1.13±0.78
E6	31^{0}18'±0.54	0.390±0.41	0.438±0.53	10.95±0.55	1.12±0.45
E7	31^{0}99'±0.67	0.400±0.34	0.454±0.44	11.89±0.22	1.13±0.33
E8	31^{0}38'±0.65	0.408±0.55	0.458±0.21	10.91±0.88	1.12±0.12
E9	30^{0}96'±0.45	0.408±0.77	0.457±0.23	10.72±0.43	1.12±0.11

All value are expressed as Mean ± Standard Deviation, n=3

The angle of repose values ranges from 30^{0}96'±0.45 to 34^{0}99'±0.12 indicating that all batches have good flow properties. The bulk density and Tapped Density values range from 0.390±0.41g/ml to 0.423±0.55 g/ml and 0.438±0.23 g/ml to 0.484±0.88 g/ml respectively indicating that the batches have good flow. The Carrs index and Hauser's Ratio values ranges from 10.72±0.43% to 15.25±0.38% and1.12±0.11 to 1.18±0.45 respectively indicates that all batches have good flow properties. From the result shown in Table No.02 of micrometrics study it was concluded that increasing concentration of polymer flow property can be improved. E9 has highest polymer concentration hence it has good flow among the all batches.

Percentage Yield:

Table 3: Percentage Yield of Microspheres of Itopride Hydrochloride

Batch No.	Practical Yield	Theoretical Yield	% Yield
E1	390±0.89	500	78±0.77
E2	520±0.88	650	80±0.78
E3	670±0.78	800	83.7±50.98
E4	525±0.65	650	80.76±0.65
E5	668±0.55	800	83.50±0.43
F6	812±0.54	950	85.47±0.33
E7	652±0.34	800	81.50±0.42
E8	820±0.23	950	86.31±0.66
E9	970±0.12	1100	88.18 ±0.24

All value are expressed as Mean ± Standard Deviation, n=3

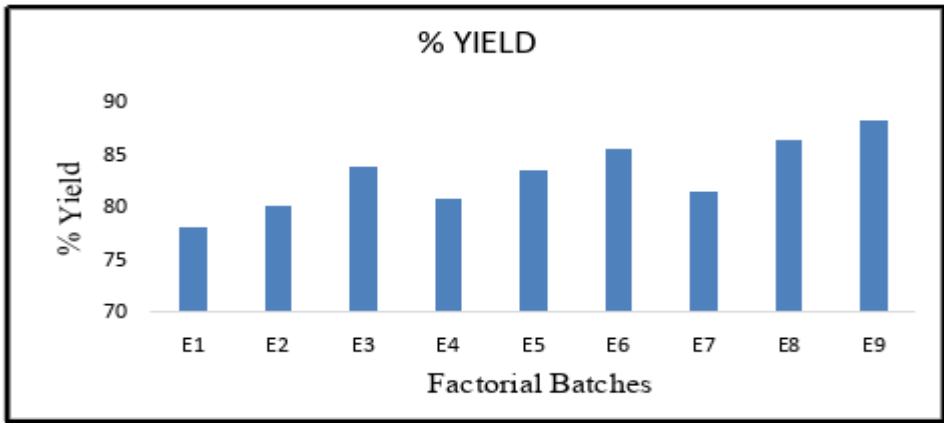

Figure 5: Percentage Yield of Microsphere of Itopride HCL

The maximum percentage yield was found in E9 formulation and was noted to be 88.18±0.24 percent yield for E1 and E9 is 78±0.77%-88.18±0.24%. The microspheres were prepared with higher concentrations of polymer has high percentage yield. Increasing concentration of polymer percent yield also increases and results are given in Table No.3 and shown in Figure No.5.

Entrapment Efficiency:

Table No.04: Entrapment Efficiency of Microsphere of Itopride HCL

Batch No.	Entrapment Efficiency (%)
E1	80.72±0.99
E2	84.44±0.77
E3	87.46±0.63
E4	81.54±0.23
E5	86.01±0.64
E6	88.39±0.78
E7	82.81±0.43
E8	86.8±0.23
E9	91.72±0.12

All value are expressed as Mean ± Standard Deviation, n=3

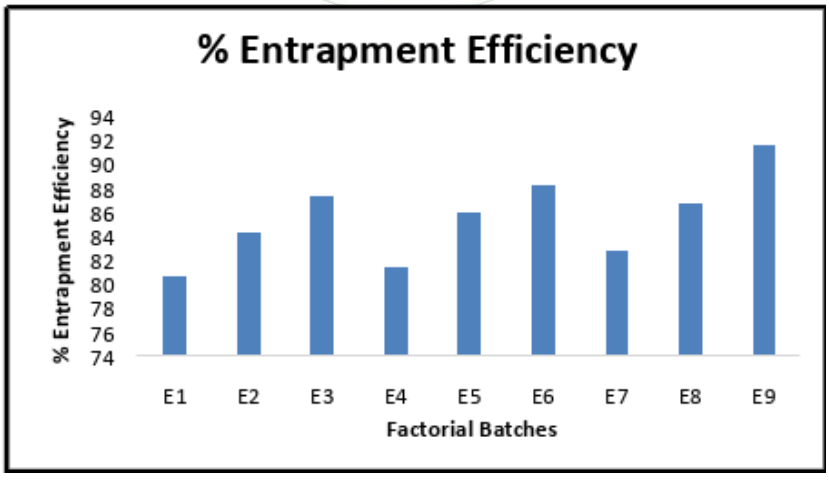

Figure 6: Entrapment Efficiency of Microsphere of Itopride

The percentage entrapment efficiency of various formulation parameters of the prepared microspheres are given in Table No. 04 and shown in Figure No.06. The entrapment efficiency varied from 80.72±0.99% to 91.72±0.12%. The formulation E9 is having high entrapment efficiency i.e. 91.72±0.12 % and E1 is having low entrapment efficiency i.e. 80.72±0.99. Increasing concentration of HPMC K100M increases the entrapment efficiency of drug.

In- Vitro Dissolution Study:

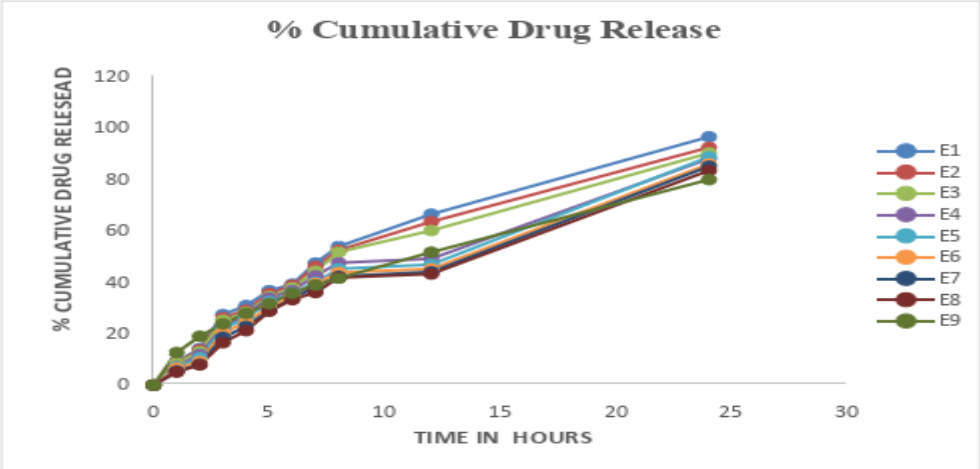

Figure 7: Dissolution Profile of All Factorial Batches

Table 5: % Cumulative Drug Release of All Factorial Batch

% Cumulative Drug Release									
T(Hr)	E1	E2	E3	E4	E5	E6	E7	E8	E9
0	0	0	0	0	0	0	0	0	0
1	9.712 ± 0.78	8.72 ±0.91	8.53 ±0.32	7.12 ±0.77	7.01 ±0.71	6.59 ±0.94	5.45 ±0.65	5.12 ±0.98	10.7 ±0.54
2	41.23 ± 0.99	13.75 ±0.90	12.98 ±0.54	11.97 ±0.89	10.64 ±0.54	9.23 ±0.54	8.12 ±0.76	7.94 ±0.99	19.05 ±0.45
3	27.45 ±0.87	26.75 ±0.87	25.21 ±0.44	22.55 ± 0.09	21.87 ±0.23	21.06 ±0.43	18.58 ±0.67	16.57 ±0.88	23.87 ±0.65
4	30.92 ±0.89	29.18 ±0.65	21.34 ±0.44	27.35 ±0.04	26.19 ±0.56	24.38 ±0.55	22.84 ±0.45	21.2 ±0.67	27.99 ±0.65
5	36.79 ±0.65	35.64 ±0.55	34.45 ±0.55	33.89 ±0.65	32.48 ±0.64	30.41 ±0.43	29.14 ±0.65	28.81 ±0.55	31.76 ±0.76
6	39.32 ± 0.56	38.45 ±0.55	37.75 ±0.44	36.78 ±0.45	30.87 ±0.44	34.69 ±0.23	33.61 ±0.33	33.34 ±0.55	35.8 ±0.89
7	47.55 ±0.65	46.71 ±0.34	45.36 ±0.76	42.54 ±0.43	40.01 ±0.56	39.53 ±0.76	38.54 ±0.55	36.11 ±0.44	39.0 ±0.88
8	54.04 ±0.55	52.56 ±0.33	51.85 ±0.76	47.65 ±0.53	45.34 ±0.78	43.89 ±0.56	42.32 ±0.44	41.87 ±0.99	41.65 ±0.54
12	66.56 ±0.44	62.65 ±0.12	60.10 ±0.43	49.28 ±0.51	46.98 ±0.99	45.26 ±0.88	44.30 ±0.55	43.83 ±0.65	51.78 ±0.54
24	96.72 ±0.55	92.97 ±0.32	90.37 ±0.14	88.24 ±0.51	88.87 ±0.33	8.12 ±0.33	83.31 ±0.44	83.57 ±0.55	80.05 ±0.54

All value are expressed as Mean ± Standard Deviation, n=3

Minimum cumulative percent drug release was found to be 80.05±0.54 for E9 batch and maximum cumulative drug release was found to be 96.75±0.55 for E1 batch. As concentration of polymer increases, it retards the release of drug upto 24 hour. As concentration of HPMC K100M increases drug release time increases. From these formulation batches E9 shows optimum release profile shown in Table No.5 and shown in Figure No.7.

Kinetics of Drug Release:

Table 6: Model Fitting Release of Factorial Batches

Batch	Zero Order	First Order	Higuchi Model	Korsemeyer Peppas Model		Hixson Crowel Model	Best Fitted Model
	R^2	R^2	R^2	R^2	N	R^2	
E1	0.9970	0.867	0.949	0.989	0.876	0.915	Zero Order
E2	0.9873	0.9937	0.9537	0.960	0.894	0.809	Korsemeyer Peppas
E3	0.987	0.982	0.940	0.996	1.005	0.908	Korsemeyer Peppas
E4	0.9835	0.995	0.9593	0.998	0.911	0.960	Korsemeyer Peppas
E5	0.984	0.981	0.945	0.990	0.987	0.916	Zero Order
E6	0.9787	0.9931	0.9478	0.978	0.911	0.998	First Order
E7	0.988	0.994	0.945	0.877	0.864	0.983	First Order
E8	0.987	0.9745	0.8799	0.891	0.984	0.964	Zero Order
E9	0.9319	0.9906	0.9927	0.670	0.530	0.988	Higuchi Model

From result of release kinetics batch E9 has Higuchi model as best fitted model with regression coefficients 0.9927 with % cumulative drug release at 24 hour is 80.05±0.54%. E9 batch has release exponent 0.530. Drug release study shows drug release from E9 batch is by Higuchi model followed by first order.

Scanning Electron Microscopy (SEM):

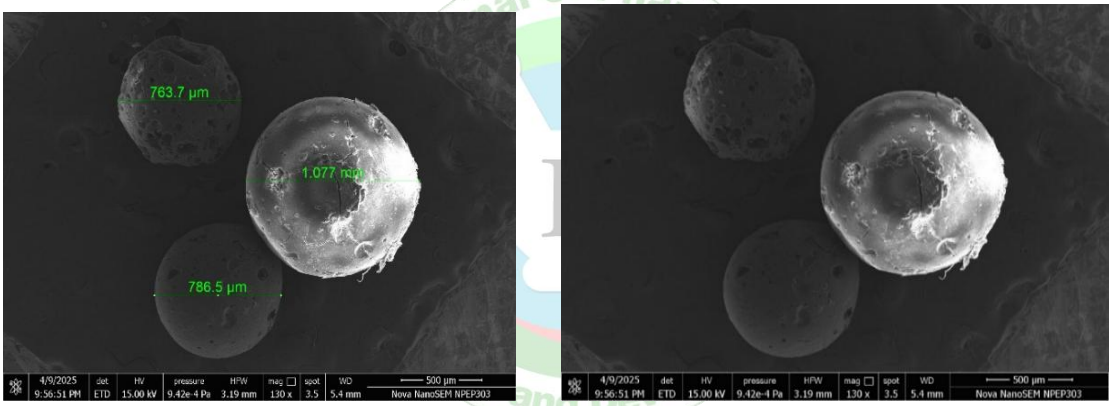

Figure 8: Scanning Electron Microscopy of Optimized Batch At 130x

The outer surface of microspheres was smooth and dense. The shell of microspheres also showed some porous structure it may be caused by evaporation of solvent entrapped within the shell of microsphere after forming smooth and dense layer. The results of Scanning Electron Microscopy of optimized batch at 130 x is given in Fig. No.8.

Zeta Potential

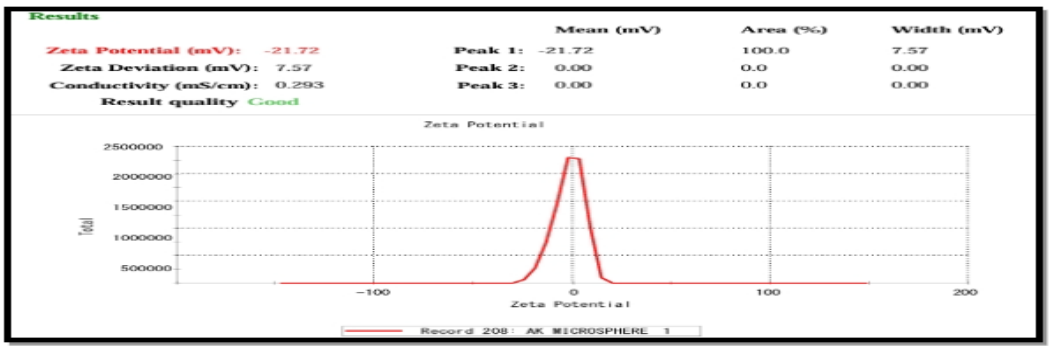

Figure 9: Zeta Potential of Optimized Batch

Figure No.9 illustrate Zeta potential for optimized batch of Oral controlled release microsphere is -21.72 mV indicating presence of optimum charge on the surface of formulations to prevent aggregation during their shelf life

Particle Size:

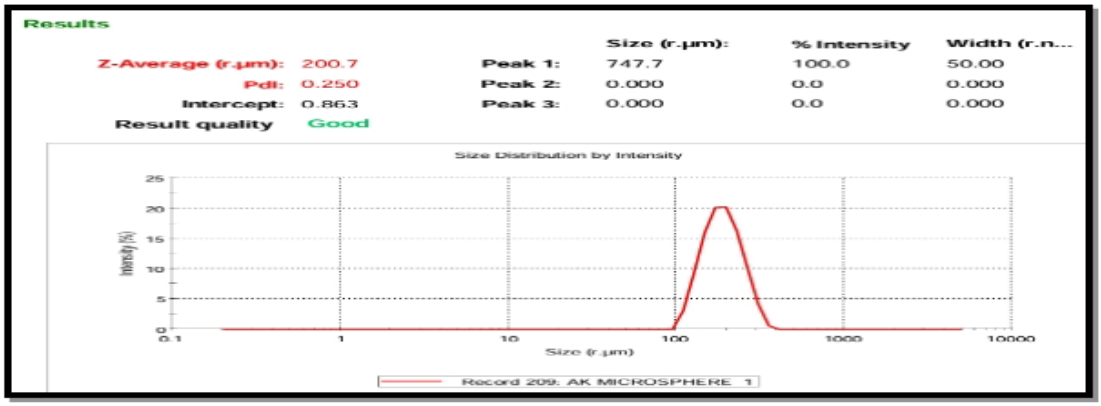

Figure 10: Particle Size Analysis of Optimized Batch

Figure No. 10 illustrate the distribution of particle sizes within a sample. The x-axis represents the size of particles, typically ranging from nanometers to micrometers, while the y-axis shows the frequency or proportion of particles within each size range. The average particle size of optimized formulation E9 was found to be 747.7 um.

Stability Study:

Table 7: Stability Study At 40^0C ± 2°C

Time	Appearance	% Drug Content	% CDR	
			After 12 Hr	After 24 Hr
0days	Spherical	91.72±0.118	51.78±0.133	80.05±0.654
1Weeks	No change	91.70±0.890	51.74±0.235	80.03±0.374
2Weeks	No change	91.69±0.765	51.68±0.337	80.03±0.878
3Weeks	No change	91.68±0.321	51.64±0.534	80.03±0.945
4Weeks	No change	91.61±0.112	51.61±0.533	80.02±0.454

All value are expressed as Mean ± Standard Deviation, n=3

Based on the results of in-vitro drug release and % drug content best formulation E9 were selected for fourweek stability studies at 40^0C±2^0C/75% RH±5%. The selected formulation were evaluated for physical appearance, % drug content and in-vitro drug release. The results showed that there was no significant change in physical appearance, % drug content and drug release profile throughout the study period. Four week of stability studies revealed that; there was no any significant degradation of the drug.Thus prepared formulations were physically and chemically stable and results are shown in Table No. 7.

CONCLUSION:

The present study has been a satisfactory attempt to formulate Controlled release microspheres of Itopride Hydrochloride with a view of improving controlled release of the drug. From the experimental results it can be concluded that, E9 is best formulation batch follow Higuchi model. Formulation E-9 contain 200 mg Itopride HCL, 450 mg of HPMC K 100M and 450 mg of Ethyl Cellulose. The result of formulation E-9 for Angle of Repose, Bulk Density, Tapped Density, Carr's Index, Hausners Ratio, Percent Yield, Drug Entrapment Efficiency, % Cumulative Drug Release, Zeta Potential, Particle Size were $30^0$96'± 0.45, 0.408±0.77, 0.457±0.23, 10.72±0.43,1.12±0.1, 88.18±0.24%, 91.72±0.12%, 80.05±0.5%, -21.72mV, 747.7 µm respectively.

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CONFLICT OF INTEREST:

All contributing authors declares no conflict of interest.

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