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Formulation & Development of Itopride Hydrochloride Microsponges For Treatment of Peptic Ulcer And GERD

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Abstract: Itopride hydrochloride is a prokinetic agent having dual mode of action used in gastroesophageal reflux disease. The aim of this investigation to develop extended release microsponges of itopride hydrochloride using Eudragit S-100 polymer to extend the drug release over longer period of time to minimize dosing frequency and side effects. Itopride hydrochloride microsponges were prepared by quasi-emulsion solvent diffusion method. Optimization were performed by response surface methodology-central composite design. The evaluation of microsponges done by different parameter such as particle size, percentage entrapment efficiency, scanning electron microscopy. The drug release was found to depends upon the polymer concentration. Thus, concluded that prepared itopride hydrochloride microsponges will be more effective and reduce dosing frequency and side effects.

Key words: **Microsponges, Itopride hydrochloride, Central Composite Design (CCD), Eudragit S-100, Quasi-emulsion solvent diffusion, Scanning Electron Microscopy (SEM), Extended release.**

1.Introduction

Gastroesophageal reflux disease (GERD) a digestive disease in which stomach acid or bile irritate the food pipe lining, this is chronic disease occurs more than 10 million cases per year in India. Acid reflux and heartburn more than twice a week may indicate GERD.

Peptic ulcer are open sores that develop on the inside lining of our stomach and the upper portion of our small intestine. Ulcers occur when stomach acid damages the lining of digestive tract. Occurs more than 1 million cases per year in India. The most common causes include the bacteria H. Pylori and anti-inflammatory pain relivers including aspirin.

Itopride hydrochloride is novel prokinetic drug have an anticholinesterase action as well as D2 receptor antagonistic action for treatment of different gastrointestinal motility disease. Itopride hydrochloride has short half life therefore selected for extended release. Extended release delivery has advantages over conventional drug delivery systems they include reduced dosing frequency, improved patient compliance and reduced GI side effects. The study was performed in order to investigate in vitro release of itopride hydrochloride from prepared extended release microsponges.

2.Materials and methods:

2.1 Materials:

Itopride hydrochloride was provided as gift sample from D. K. Pharmachem Pvt. Ltd, Mumbai. Eudragit S-100 was purchased from Analab fine chemicals, Mumbai. Other chemical and excipients used were of analytical reagent available at Dr. D. Y. Patil College of Pharmacy laboratory of Pharmaceutics.

2.2 Methods:

2.2.1 Pre-formulation studies:

Pre-formulation study is the process in the development of dosage form of a drug substance. It is characterised by physical and chemical properties of drug and drug with excipients. Such as physical appearance, solubility, melting point, UV-Analysis, compatibility study by FT-IR.

2.3 Experimental design:

Response surface methodology is one of the methods in the development and optimization of drug formulations. Based on aim of design of experiments (DOE). This methodology involves generation of polynomial mathematical relationship and mapping of response to pick the optimum formulation. Central composite design (CCD) with 3^2 is one of designs available for statistical optimization of the formulations.

Optimization of microsponges were performed using central composite design. This design was carried out by design expert-12 software for review effects of independent variables.

2.4 Development of microsponges by quasi-emulsion solvent diffusion method

Microsponges were formulated by a quasi-emulsion solvent diffusion method using an internal phase containing polymer which is dissolved in dichloromethane/ethyl alcohol. Then the active drug is added to the polymer solution and dissolved under ultra-sonication at 35 °C. The inner phase is then transfer into external phase containing polyvinyl alcohol and distilled water with continuous stirring for 3 hr. The mixture was filtered and separate the Microsponges. The obtained product was washed and dried in an air heated oven at 40 °C for 12 hr.

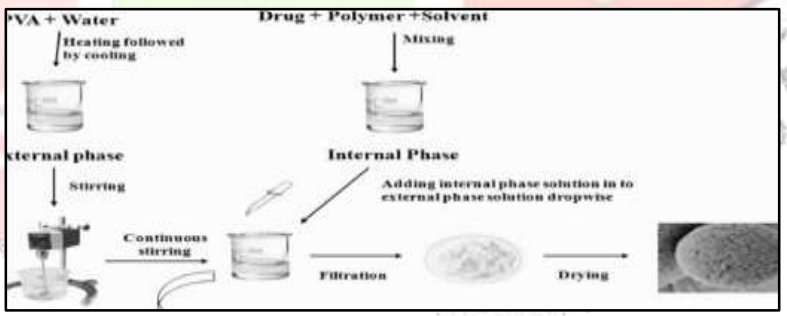


Figure 1: Process of quasi-emulsion solvent diffusion method

Figure 2: Typical diagram of microsponge

Table 1: Formula for Itopride hydrochloride microsponge

Sr. no.	Formulation code	Itopride hydrochloride (mg)	Eudragit S-100 (%)	PVA (%)	NaCl (%)	DCM (ml)	Water (ml)
1	F1	150	12.5	0.25	1	15	100
2	F2	150	5	0.50	1	15	100
3	F3	150	20	0.50	1	15	100
4	F4	150	1.89	0.25	1	15	100
5	F5	150	23.10	0.25	1	15	100
6	F6	150	12.5	0.60	1	15	100
7	F7	150	12.5	00	1	15	100
8	F8	150	5	00	1	15	100
9	F9	150	20	00	1	15	100

3.Evaluation parameter of microsponges

3.1 Flow properties:

3.1.1 Bulk Density: In this method microsponge are transferred to a measuring cylinder and is tapped manually till a constant volume is obtained. This volume is bulk volume and it includes true volume of the powder and the void space among the microsponge.

Bulk density was calculated by following formula;

B.D. = mass of microsponge/bulk volume

3.1.2 Tapped Density: In this method microsponge were transferred to a measuring cylinder and tapped for 100 times. After tapping volume of microsponge was visually examined. The ratio of mass of microsponge to volume of microsponge after tapping gives tapped density

T.D. = Mass of microsponge/tapped volume

3.1.3 Car's index: Car's index or compressibility index of the powder blend was determined by Car's compressibility index.

Car's index = Tapped density – Bulk density / Tapped density *100

The compressibility index values calculated and correlated with standard values.

3.1.4 Hausners Ratio: Hausners ratio was determined from the ratio of tapped density to bulk density using formula are follows:

Hausners ratio = Tapped density / Bulk density

3.1.5 Angle of Repose: This is maximum angle possible between surface of pile of powder or granules and the horizontal plane.

Angle of repose was calculated using the following equation;

$$\tan\theta=(h/r)$$

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

Where,

θ = Angle of repose

h = height of heap of granules

r = radius of heap of granules.

3.2 Particle size: The particle size was measured by microscopic technique in this method the microsponge formulation was mounted on a slide and observed under optical microscope. About 100 particles were measured with the help of eye micrometre. All the microsponge in a field were counted.

3.3 Percentage yield: The prepared microsponge with size range from 50-400um were weighed accurately and measured weight was divided by total amount of all non-volatile components.

The percentage yield was calculated by following formula;

$$\% \text{ yield} = \text{Actual yield/Theoretical yield} \times 100$$

3.4 Percentage entrapment efficiency: The entrapment efficiency (%) is calculated using the following equation;

$$\% \text{ EE} = \text{Actual drug loading/Theoretical drug loading} \times 100$$

3.5 Scanning electron microscopy (SEM): For the surface topography and morphology prepared microsponges was coated with gold palladium under an argon atmosphere at room temperature and morphology were studied by scanning electron microscopy. SEM can be illustrating its ultra-structure.

3.6 In vitro drug release studies:

Apparatus: USP Type ll/paddle type apparatus

Media: 900 ml of 0.1N HCl for initial 2 Hours, then Phosphate Buffer pH 6.8

Time intervals: 0, 30, 60, 90, 120, 150, 180,240, 300, 360, 420 minutes.

Temperature: $37^0C \pm 0.5^0C$

The in vitro drug release from capsules was carried out using USP type ll apparatus at 50 rpm and $37^0C \pm 0.5^0C$. 0.1N hydrochloric acid after 2 hours replace 0.1 N HCl with phosphate buffer 6.8 pH was used as the dissolution medium. 1 ml of dissolution medium was withdrawn at pre-determined time intervals and fresh dissolution medium was replaced. The samples were withdrawn at regular intervals and analysed by UV spectrophotometer at 258 nm.

4.Results and discussion:

4.1 Physicochemical properties of drug

Table 2: Physical properties of drug

Physiochemical properties	Itopride hydrochloride	
	Reported	Observed
Appearance	White to off white in color.	White to off white in color
Melting point	193-194^{0}C	193.5^{0}C

The melting point was found within the range of 193-194^{0}C by capillary method.

4.2 Solubility of drug

Solubility of the drug were performed in different solvents for selection of suitable solvent to dissolve drug. Solubility of drug may depend on temperature, pH, ionic strength.

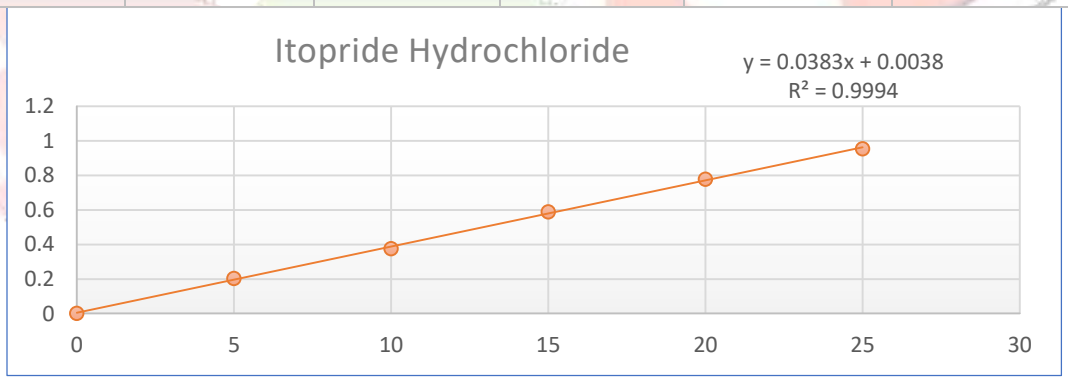
Table 3: Solubility study

Solvent	Solubility
Distilled water	Soluble
Methanol	Soluble
Ethanol	Sparingly soluble
Phosphate buffer 6.8	Sparingly soluble

4.3 UV-visible spectroscopy

Table 4: Determination calibration curve of itopride hydrochloride in distilled water

Conc (µg/ml)	Absorbance 1	Absorbance 2	Absorbance 3	Mean Absorbance	S.D.
0	0	0	0	0	0.0000±0
5	0.203	0.202	0.202	0.202	0.202±0.001
10	0.377	0.376	0.376	0.376	0.376±0.001
15	0.587	0.588	0.588	0.588	0.588±0.001
20	0.777	0.777	0.776	0.777	0.777±0.001
25	0.953	0.953	0.954	0.954	0.954±0.001

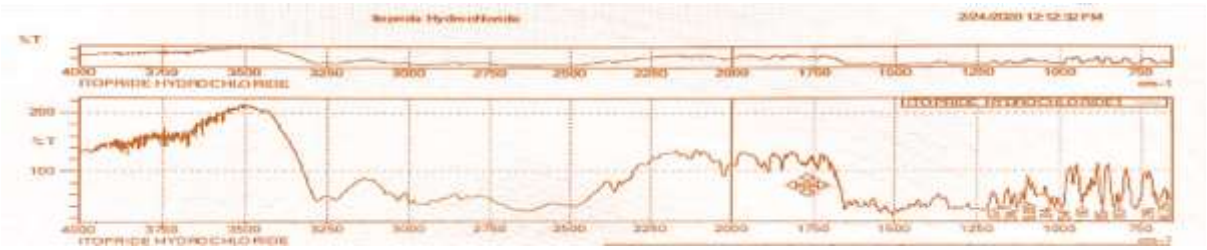


Graph 1: Calibration Curve of itopride hydrochloride at 258nm in distilled water

UV-visible spectroscopy was performed to determine calibration curve of itopride hydrochloride to characterise the pure drug and determine ƛ max of drug. The ƛ max was found at 258nm.

4.4 FT-IR Studies

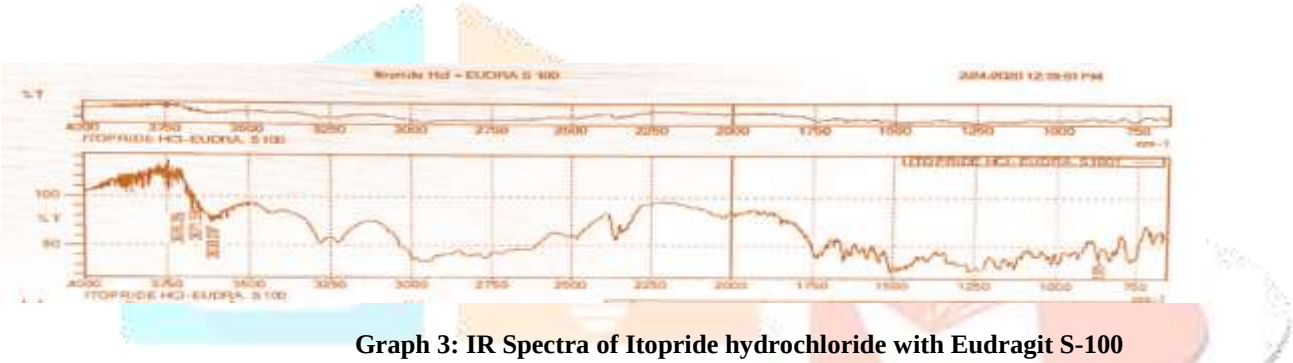
FT-IR study of drug was performed for identification and to characterise the pure drug on the basis of absorption and position of peak in IR.



Graph 2: IR Spectra of Itopride hydrochloride

4.5 Drug - Excipient Compatibility Study

Drug and Excipients compatibility study on the basis of FTIR spectra is shown in **graph 3 & 4.** The spectra shown there is no difference in the absorption and position of peak in IR. This shown that there is no any chemical interaction between Drugs and Excipient.
This study indicated that drug and excipients combination are stable.



Graph 3: IR Spectra of Itopride hydrochloride with Eudragit S-100

Graph 4: IR Spectra of Itopride hydrochloride with Polyvinyl Alcohol

4.5 Particle Size

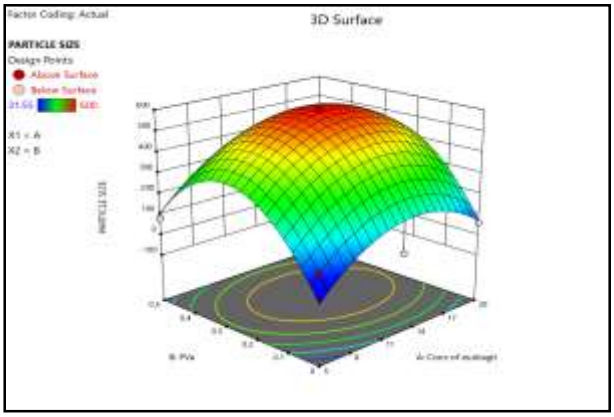


Figure 3: 3D response surface plot for effect of concentration of Eudragit S-100 and polyvinyl alcohol on particle size

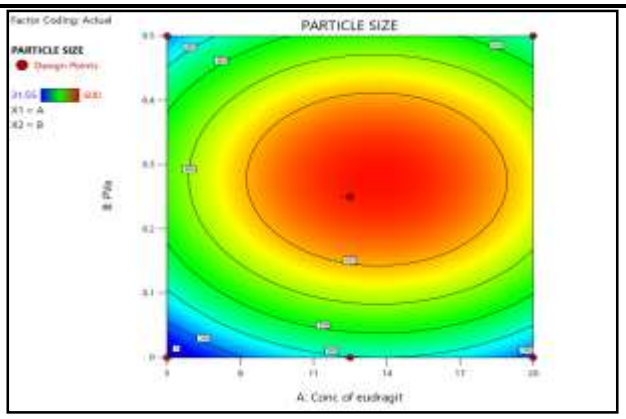


Figure 4: Contour plot for effect of concentration of Eudragit S-100 and polyvinyl alcohol on particle size

ANOVA test for the observed data of particle size of microsponge indicate that the quadratic model was significant and fitting for the data. P value less than 0.0050 and F value of 9.40 indicate model terms are significant. Final equation in terms of coded factors,

Polynomial equation = +584.55 +53.52a +70.14b-5.08ab-182.10a^2-319.24b^2

4.6 % Entrapment Efficiency

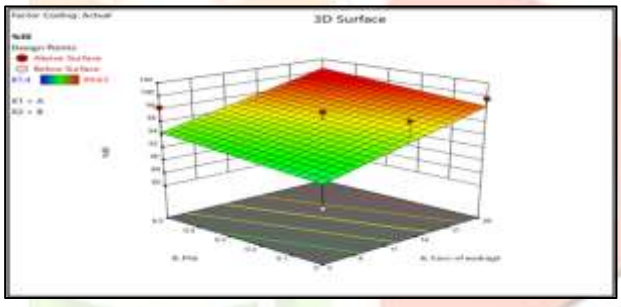


Figure 5: 3D response surface plot for effect of concentration of Eudragit S-100 and polyvinyl alcohol on %entrapment efficiency

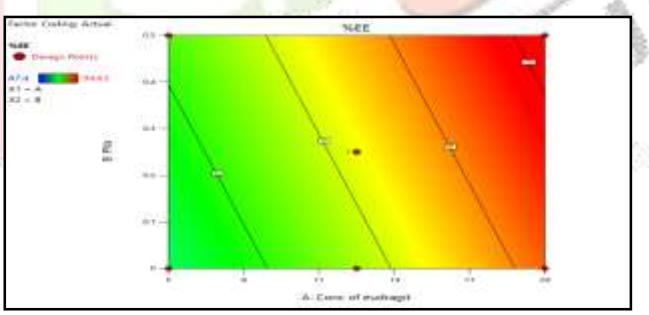


Figure 6: Contour plot for effect of concentration of Eudragit S-100 and polyvinyl alcohol on %entrapment efficiency

ANOVA test for the observed data of percent entrapment efficiency of microsponge indicate that the quadratic model was significant and fitting for the data. P-values less than 0.0500 and F-value of 4.48 indicate model terms are significant. Final equation in terms of coded factors,

Polynomial equation= +96.46 +3.04a +1.01b

4.7 Evaluation of microsponges:

Table 5: Flow properties of microsponges

Formulation code	Bulk density	Tapped density	Hausners ratio	Car's index	Angle of repose
F1	0.443	0.510	1.15	13.13	27.36
F2	0.293	0.363	1.23	19.28	23.56
F3	0.534	0.635	1.18	15.90	29.12
F4	0.151	0.222	1.47	31.98	25.63
F5	0.665	0.752	1.13	11.56	31.35
F6	0.363	0.424	1.16	14.38	28.26
F7	0.535	0.609	1.13	12.15	32.21
F8	0.428	0.761	1.17	30.61	24.89
F9	0.640	0.707	1.10	9.47	26.58

Table 6: Particle size, % entrapment efficiency, percentage yield

Formulation code	Particle size um (mean)	% Entrapment efficiency	Percentage yield
F1	300	97.60	83.20
F2	81.60	98.29	84.88
F3	31.55	96.38	84.76
F4	58.83	87.40	49.85
F5	318	98.40	79.44
F6	158.6	98.69	88.04
F7	40.70	98.60	87.25
F8	88.67	88.96	76.11
F9	88.83	99.63	85.39

4.8 Scanning electron microscopy (SEM)

scanning electron microscopy (SEM) were used for determine the shape and surface morphology of microsponge. The microsponges observed by SEM analysis was spherical in shape having numerous pores on surfaces of microsponge

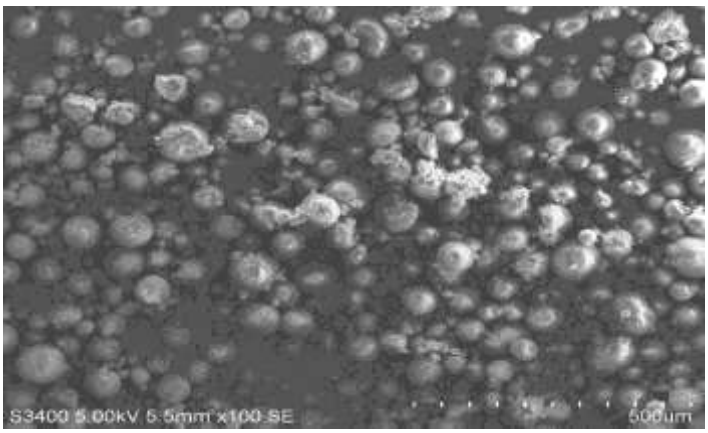
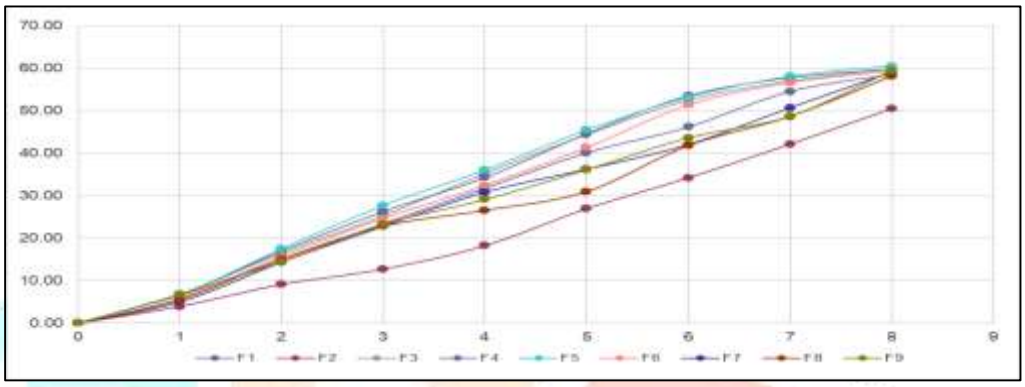


Figure 7: Scanning electron microscopy of itopride hydrochloride microsponges

4.9 In vitro drug release:

Table 7: % Drug Release Observation Table

Time (hours)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	6.54	3.94	6.80	6.75	6.78	5.90	5.0	5.54	6.78
2	15.00	9.12	16.45	16.95	17.49	15.71	14.37	15.08	14.44
3	23.44	12.72	25.29	26.29	27.72	24.68	22.84	23.81	23.24
4	31.76	18.25	34.27	34.27	36.07	32.47	30.82	26.56	27.12
5	40.10	26.95	44.10	44.59	45.50	41.36	38.23	30.97	35.13
6	46.19	34.22	52.48	53.55	53.16	51.38	42.06	41.82	43.63
7	54.57	42.15	57.03	57.77	58.14	56.63	50.71	48.67	48.70
8	58.52	50.51	59.85	59.85	60.60	59.29	59.11	58.20	59.46



Graph 5: Cumulative % drug release of Itopride hydrochloride from different microsponge formulation

The in vitro drug release of microsponges were studied using USP Type ll apparatus keeping stirring rate 50rpm. Temperature maintained at 37^0C $\pm$ 0.5^0C. Drug release were carried out in 900ml phosphate buffer (pH 6.8). analysed spectrophotometrically at λ max 258 nm.

5.Conclusion:

In the present study itopride hydrochloride microsponges were successfully developed in the form of extended release to improve the drug release. Microsponges were prepared by using Eudragit S-100 as release retarding polymers for controlled release. FT-IR studies shown that there no chemical interaction between drug and excipients used in the formulation. The flow properties of microsponges were within the acceptance/ good range.

Among all the formulations F2 was found to be the best formulations as release drug over extended period of time

By the dug release studies optimized F_2 formulation was concluded that the drug release profile was maximum.

Hence, it was concluded that the prepared microsponges of itopride hydrochloride may safe and effective controlled drug delivery over extended period of time also can reduce dosing frequency.

6.Acknowledgements: Authors would like to thanks D.K. Pharmachem Pvt. Ltd, Mumbai for providing a gift sample of Itopride hydrochloride.

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