Formulation and evaluation of Metoclopramide hydrochloride floating microsphere

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Abstract : Metoclopramide hydrochloride is used as dopamine receptor antagonist antiemetic and for achieving long term effect there is need to give Metoclopramide hydrochloride as sustained drug delivery.The objective of the present study was to formulate and evaluate floating microspheres for metoclopramide hydrochloride for prolonged buoyancy with sustained release of the drug into the gastric content. Metoclopramide hydrochloride loaded microspheres were prepared by the solvent evaporation method using 3^2 factorial design .all the formulation shows good micromeritic properties. Percentage yield of all formulation varied from 76.84% to 93.77% where F1 has 76.84% and F9 has 93.77%. This shows that as polymer conc. and rpm increases; percentage yield also increases. *In vitro* drug release of all formulation varied from 67.14% to 83.69%. The optimized formulation exhibited % drug entrapment efficiency of 88.82%, 73.99% of in vitro buoyancy after 12 hr and 80.31% drug release. From the solution for optimization as per Design Expert Software it can be concluded as F7 formulation is the best formulation**.**

keywords **- floating microsphere, metoclopramide hydrochloride, HPMC K15M,Eudragit S100 ethyl cellulose, sustained release**.

I. INTRODUCTION

An ideal dosage form is one, which attains the desired therapeutic concentration of drug in plasma and maintains constant for entire duration of treatment When conventional immediate release dosage forms are taken on schedule and more than once daily, they cause sequential therapeutic blood level peaks and valleys associated with the taking of each dose. However, when doses are not administered on schedule, the resulting peaks and valleys reflect less than optimum drug therapy. In contrast to conventional forms, modified release products provide either delayed release or sustained release of drug. Sustained release products are designed to release their medication in a controlled manner, at a predetermined rate, duration and location to achieve and maintain optimum therapeutic blood levels of drug. The US FDA defines sustained release dosage form as 'one that allows reduction in dosing frequency from that necessitated by a conventional dosage form.[1, 2]'

The concept of FDDS was described in the literature as early as 1986, when Davis discovered a method for overcoming the difficulty experienced by some persons of gagging or choking while swallowing medicinal pills.

Floating microspheres are gastro-retentive floating drug delivery systems based on non-effervescent approach. These microspheres are characteristically free flowing powders having a size less than 200 µm and remain buoyant over gastric contents and for prolonged period. As the system floats over gastric contents, the drug is released slowly at desired rate resulting in increased gastric retention with reduced fluctuations in plasma drug concentration.[5]

Metoclopramide hydrochloride in its conventional dosage forms like tablets and injections produce many side effects like chills, convulsions, dizziness or fainting, fast or irregular heartbeat, headache, increasing blood pressure, increased swelling itching, skin rash and loss of appetite. Metoclopramide needs to be administered 2-3 times daily, which may lead to patient non-compliance.[6] These limitations associated with Metoclopramide administration may be overcome by modifying the drug delivery systems. Among the various drug delivery systems available, floating drug delivery system provides many benefits like extended period of drug action, increased bioavailability and increased patient compliance.[6]Metoclopramide Hydrochloride is D2 receptor antagonist and for achieving long term effect there is need to give Metoclopramide hydrochloride as sustained drug delivery also have short half-life about 5-6 hrs Bioavailability is upto 60-70% Unstable in alkaline pH and stable in acidic environment and has absorption window in the upper part of GIT. Thus Metoclopramide HCl is suitable candidate for Floating microspheres.

II. MATERIALS AND METHODS

The drug, Metoclopramide Hydrochloride was procured as gift sample from IPCA Ltd, Mumbai, Maharashtra, India. Ethanol from S.D Chemicals, Eudragit S 100(ERS) Rohm lab,Germany and Hydroxyl propyl methyl cellulose K-15M. Obtained as gift sample form Wockhardt ltd

2.1. Preparation of Metoclopramide hydrochloride floating microspheres

All preliminary batches for Metoclopramide hydrochloride floating microspheres were prepared of different polymer composition such as Eudragit S100 and hydroxyl propyl methyl cellulose K15M, stirring speed was varied and drug weights was kept constant and were evaluated for various parameters [7]

Polymer composition in ratio for various batches						
Materials	MG1	MG2	MG3	MG4	MG5	MG6
HPMC K15M	0	2	1	4	2	3
Eudragit S100	1	2	0	2	4	1
Stirring speed	900	1200	1200	1200	900	900

Table 2.1.1: Polymeric composition for preparation of preliminary trial batches

2.2. Formulation of Metoclopramide hydrochloride floating microspheres

Weighed amount of polymer and drug were dissolved in combination of ethanol: dichloromethane (1:1) at room temperature. This drug-polymer solution was slowly poured into 250 ml water containing 0.02% Tween 80 as stabilizer. N-hexane (porosity generator) was added to above solution and shaken .Solution was stirred at 1200 rpm with magnetic stirrer for 2 hrs to allow the evaporation of volatile solvent and prepared microsphere were filtered, washed with distilled water and dried in vacuum oven.[7] Formulation composition of optimized batch from preliminary trial batches results were tried using 3^2 factorial design given below.

Ingredient	Use	Quantity
Metoclopramide hydrochloride	API	140 mg
HPMC K15M	Coating polymer	700 mg
Eudragit S100	Coating polymer	350 mg
Ethanol: dichloromethane	Solvent	10:10(ml)
N-hexane	Porosity generator	1 ml
Distilled water	As a continuous phase	q.s.
Tween 80	Stabilizer	0.02%

Table 2.2.1: Formula of optimized batch at 1200 rpm from preliminary trial

A 3^2 factorial design was applied to prepare floating microspheres. HPMC K15 M and Eudragit S100 ratio, stirring speed were independent variables and drug weight was kept constant and effect of independent variable was checked on evaluation parameters. Method for factorial batches formulation was same as preliminary batches.

Variables	Levels		
	Lower (-1)	Middle (0)	Upper (+1)
X_1:Ratio of HPMC K15M:Eudragit S100	3:2	4:2	5:2
X_2:stirring speed	900	1200	1500

Table 2.2.2: Variables and their levels for factorial design

Formulation	X1	X2
F1	-1	-1
F2	-1	0
F3	-1	+1
F4	0	-1
F5	0	0
F6	0	+1
F7	+1	-1
F8	+1	0
F9	+1	+1

Table 2.2.3: Formulation of floating microspheres

2.3. Preformulation study:

2.3.1. Metoclopramide hydrochloride

Various tests were carried out on the sample of the drug to establish its identity and purity and the results were compared with specifications reported in literatures, wherever possible. The parameters studied include:

Identification Test

1. FTIR analysis

The identification of Metoclopramide hydrochloride was done by FTIR spectroscopy.FTIR spectrums were recorded using an FTIR-4100 spectrophotometer (Jasco Corporation, Japan). The wavelength ranged from 400 to 4000 cm^{-1} with a resolution of 4 cm^{-1}.[8]

2. Description

The drug sample was analyzed for physical appearance, color and odor.

3. Melting point

The melting point of Metoclopramide hydrochloride was recorded by capillary method using Thiele's tube melting point apparatus and was compared with the literature reported data.[8]

4. Solubility

The solubility of the drug was evaluated by dissolving drug in water and ethanol[8]

2.3.2. Characterization of Excipients

Polymers and other excipients used in the study were standardized as per Handbook of Pharmaceutical Excipients, for their physiochemical characteristics such as appearance, solubility, pH, melting point .[9,10]

2.3.3. Drug Excipients Compatibility Study

2.3.3.1. FTIR analysis

Physical mixture comprising of drug and HPMC, as well as Eudragit S-100 in equal ratios were dispensed in a 2 ml vial. The sample was stored at 40 ^{0}C for 6 days to accelerate the interactions between drug and excipients.[11]

2.3.3.2. DSC analysis

Differential scanning colorimetry (DSC) analysis was performed for pure drug using a DSC, Shimadzu TA 60WS, instrument. Equal ratios of physical mixture of drug and polymer were mixed thoroughly for 5 min in mortar. The materials were then stored at 40 ± 2°C, 75% relative humidity for 4 weeks. Each sample was accurately weighed (~1-3 mg) in an aluminum pan, crimped, and hermetically sealed, while an empty pan of the same type was used as a reference. The system was calibrated with high purity sample of Indium. The samples were scanned at the heating rate of 20^0C/min over a temperature range of 100 to 300 ^{0}C under the nitrogen atmosphere.[12]

2.4. Method of Drug Analysis

2.4.1. Preparation of standard stock solution

Standard drug solution of Metoclopramide hydrochloride was prepared by dissolving 10 mg of drug in simulated gastric fluid (p^H 1.2) and volume was made up to 100 ml to obtain stock solution of 100µg/ml concentration.[13]

2.4.2. Generation of calibration curve

Aliquots of 0.5 to 3.0 ml portion of stock solutions were transferred to series of 10 ml volumetric flasks, and volume made up to mark with simulated gastric fluid (pH 1.2)Solutions were scanned in the range of 200-400 nm against blank. The absorption maxima were found to be at 272 nm against blank. The calibration curve was plotted[13].

2.5. Evaluation of floating microspheres

2.5.1. Micromeritics:

Microspheres were characterized for their micromeritics properties such as particle size, angle of repose, compressibility index and Hausner's ratio[14,15].

2.5.2. Percentage yield

Percentage yield of floating microspheres was calculated by dividing actual weight of product to total amount of all non-volatile components that are used in the preparation of floating microspheres and is represented by following formula[7]

% yield = (actual weight of product/total weight of drug and Excipients) ×100

2.5.3. Drug entrapment efficiency (DEE)

Estimation of drug content in floating microspheres was carried out by dissolving the weighed amount of crushed microspheres in required quantity of 0.1 N HCl then filtered and analyzed spectrophotometrically at a 272 nm using the calibration curve. Each batch was examined for drug content in a triplicate manner.[16]

DEE = (amount of drug actually present/theoretical drug load expected) × 100

2.5.4. In vitro Buoyancy

Floating behavior of hollow microspheres was studied using a USP dissolution test apparatus II by spreading the microspheres (50 mg) on 900 ml of 0.1 N HCl containing 0.02% Tween 80 as surfactant. The medium was agitated with a paddle rotating at 100 rpm and maintained at 37°C. After 12 hours, both the floating and the settled portions of microspheres were collected separately. The microspheres were filtered, dried and weighed. The percentage of floating microspheres was calculated using the following equation[7]

Fig.2.5.4.1: In vitro buoyancy of floating microspheres Metoclopamide hydrochloride

% buoyancy of microspheres = (weight of floating microspheres/initial weight of floating microspheres) x 100

2.5.5. Dissolution test (in vitro-drug release) of microspheres

The dissolution medium used was 900ml of 0.1 N HCl (pH 1.2) with 100 rpm speed at 37 ± 0.5^0C).The 5 ml samples were withdrawn from dissolution media at predetermined time interval (1 h) carried out upto 12 hr then filtered using Whatman filter paper. Samples were analyzed for drug at 272 nm using a UV visible double beam spectrophotometer[7, 17]

2.5.6. Kinetic analysis of *in vitro* drug release data

The dissolution profile of all the batches were fitted to zero order kinetics, first order kinetics, Higuchi, Hixson-Crowell, Korsmeyer and Peppas to ascertain the kinetic modeling of drug release by using a PCP Disso Version 2.08 software, and the model with the higher correlation coefficient was considered to be the best model

In order to know the drug release mechanism the data was further analyzed by Korsmeyer Peppas equation and the value of n i.e. release exponent was calculated.

2.5.7. Morphological Study using SEM

The external and internal morphology of the microspheres were studied by scanning electron microscopy (SEM).[7]

2.5.8. Stability Studies

Optimized formulation was sealed in aluminum packaging, coated inside with polyethylene. The samples were kept in the stability chamber maintained at 40°C and 75% RH for 3 months. At the end of studies, samples were analyzed for the physical appearance and drug content.[7, 17]

2.5.9. Multiple regression analysis of 3^2 factorial batches

The responses obtained from 3^2 factorial batches were subjected to multiple regression analysis. The polynomial equations were determined using the form[18]

$$Yi= b_0+b_1X_1+b_2X_2+ b_{11}X_1^2+ b_{22}X_2^2 + b_{12}X_1X_2+ b_{12} X_1 X_2^2+ b_{12} X_1^2 X_2+ b_{12} X_1^2 X_2^2$$

Where Yi is the dependent variable, b_0 is the arithmetic mean response of the 9 runs, and b_1 is the estimated coefficient for the factor X_1. The main effects (X_1 and X_2) represent the average results of changing one factor at a time from its low to high value.

The term X_1^2 and X_2^2 indicate curve linear relationship. The interaction X_1X_2 shows how the dependent variable changes when two or more factors are simultaneously changed. The targeted response parameters were statistically analyzed by applying one-way analysis of variance (ANOVA) at 0.05 levels in Design-Expert 7.1.6 version soft ware (Stat-Ease Inc., Minneapolis, MN).

III. Result and discussion

3.1.Preformulation study

3.1.1. Characterization of Metoclopramide hydrochloride

Test	Specifications[8]	Results
Colour	White	Confirms
Odour	Odourless	Confirms
Physical state	Powder	Confirms
Identification	FTIR	Positive
Melting point	(147°C-150°C)	150^{0}C
pH of 10% water solution	4.6-6.5	5.0
Log P	1.4	Confirms
Solubility	Soluble in water, ethanol	Confirms

Table 3.1.1.1: Characterization of Metoclopramide hydrochloride

3.1.2. FTIR spectrum of Metoclopramide hydrochloride

FTIR absorption spectrum of Metoclopramide hydrochloride was taken and the spectral assignments for major bands were in consistent with the structure of Metoclopramide hydrochloride.

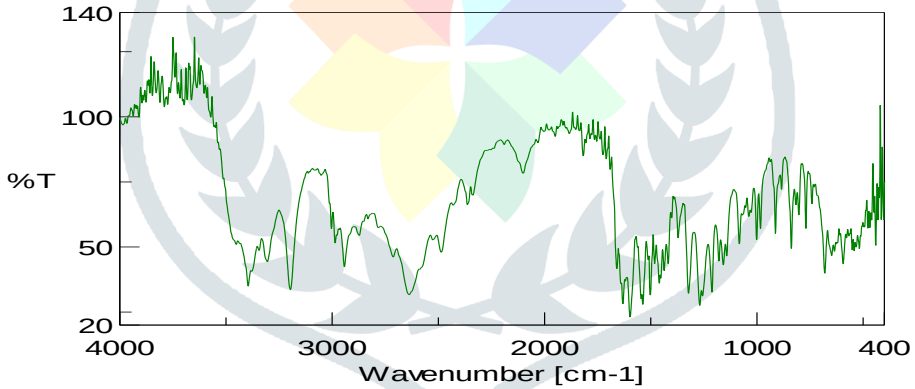


Fig. 3.1.2.1: FTIR spectra of Metoclopramide hydrochloride

Sr. No.	*Functional Group*	Frequency(cm^{-1})
1	C=O	1600
2	N-H	3300, 3340, 3400, 3460
3	NH (Amide)	1540
4	C-O	1270
5	C-Cl	700

Table**3.1.2.1:** Spectral assignment of Metoclopramide hydrochloride

3.1.3.Drug excipient compatibility (Drug+ Eudragit S100+HPMC K15M) [11]

Drug-excipients interaction study was done to find the possible interaction if any, between drug and excipients. The FTIR spectra of individual polymer, drug and physical mixture were taken. Spectra of individual polymer and drug sample were compared with the spectra of physical mixture. The FTIR spectra of physical mixture showed clearly the characteristic peaks of drug and polymer.

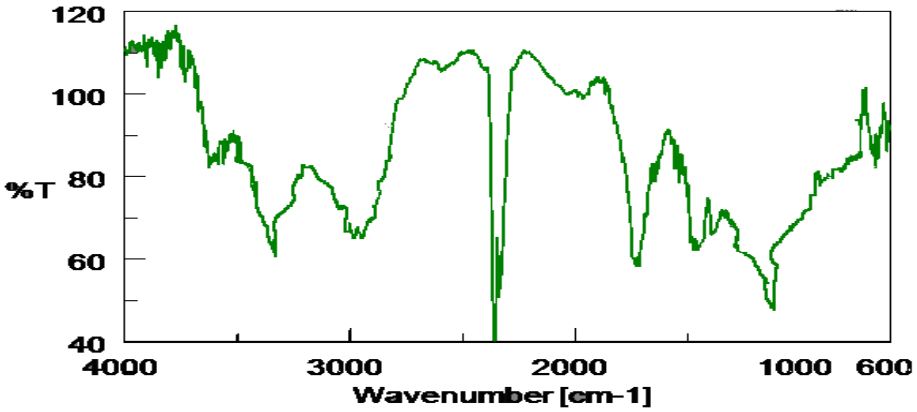


Fig.3.1.3.1: FTIR spectra of Drug+ Eudragit S100+HPMC K15M (1:1:1)

Sr. No.	*Functional Group*	Frequency(cm^{-1})
1	C=O	1600
2	N-H	3300, 3340, 3400, 3460
3	NH (Amide)	1540
4	C-O	1270
5	C-Cl	700
6	C-C stretching	1266
7	C-O-C stretching	1078
8	C-H stretching	2892

Table 3.1.3.1: Spectral assignment of Drug +Eudragit S100+HPMC K15M (1:1:1)

3.1.4. DSC of Metoclopramide hydrochloride

DSC thermogram of Metoclopramide hydrochloride was similar to that given in Analytical profile of drug substances by Florey. DSC thermogram of Metoclopramide hydrochloride showed an endothermic peak at 150^0C corresponding to the drug's melting point

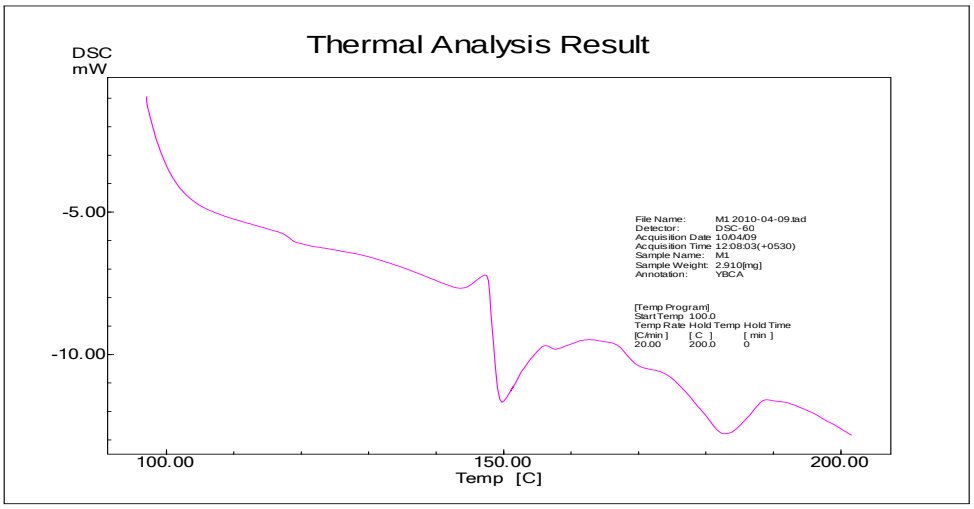


Fig.3.1.4.1: DSC thermogram of Metoclopramide Hydrochloride

3.2. Method of drug analysis

3.2.1. Solubility

Solubility of drug in water at room temperature was found to be 10 mg/ml

3.2.2. Construction of calibration curve

Calibration curve of Metoclopramide hydrochloride was taken at λ_{max} 272 nm in pH 1.2[19]

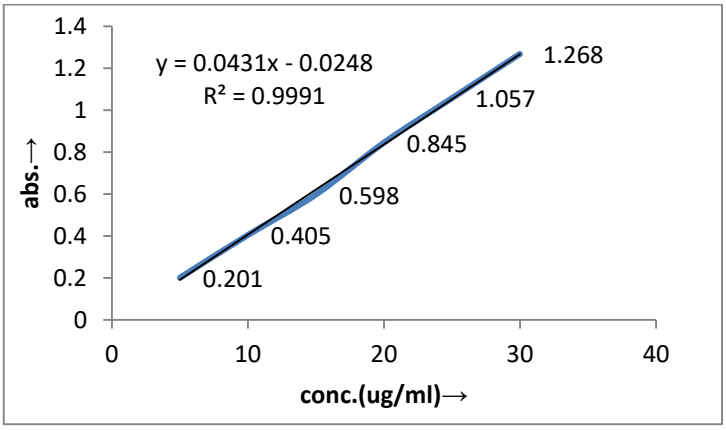


Fig.3.2.2.1: Calibration curve of Metoclopramide hydrochloride in 0.1 N HCl

3.3. Formulation development

A 3^2 factorial design was applied for preparing Metoclopramide hydrochloride floating microsphere and to study the effect of independent variables i.e. ratio of HPMC K15M and Eudragit S100[X_1 (mg)] and Stirring speed [X_2 (rpm)] on various responses i.e. *in vitro* drug release, % drug entrapment efficiency, percentage yield and *in vitro* buoyancy.

3.3.1. Physical Characterization of floating microspheres

Sr.No.	Characteristics	Observation
1	Appearance	Spherical , light weight
2	Color	White
3	Odour	Odourless
4	Shape	Round

Table 3.3.1.1: Physical Characterization of floating microspheres

Fig.3.3.1.1: Floating microspheres

All the microspheres were studied under optical microscope using optics at 10 X magnification for sphericity and all microspheres shows spherical shape

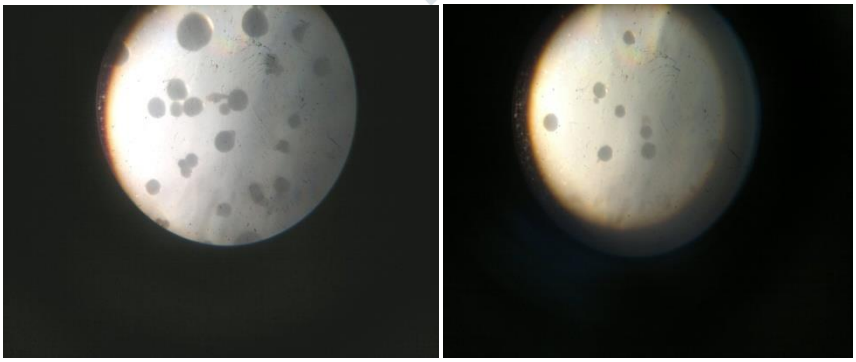


Fig.3.3.1.1: Image using optics showing sphericity of hollow microspheres at 10X magnification

3.3.2. Evaluation of floating microspheres

3.3.2.1. Micromeritic properties of floating microsphere

Batch code	Mean particle size(µm)	Bulk density (gm/ml)	Tapped density (gm/cm^3)	Carr's index (%)	Hausner's ratio	Angle of repose(θ)
F1	157.2±1.59	0.52±0.02	0.58±0.02	10.34±0.62	1.10±0.01	28.16±0.92
F2	142.34±1.98	0.48±0.02	0.53±0.02	9.43±0.46	1.10±0.01	29.02±0.93
F3	125.21±.1.45	0.47±0.03	0.52±0.03	9.61±0.53	1.11±0.01	28.51±0.85
F4	178.05±1.43	0.47±0.02	0.52±0.02	9.61±1.28	1.09±0.02	27.74±0.78
F5	166.3±2.96	0.47±0.02	0.52±0.02	9.61±0.33	1.10±0.01	28.20±1.22
F6	152.7±1.87	0.46±0.03	0.51±0.03	9.80±0.35	1.11±0.01	28.59±0.99
F7	186.41±1.18	0.48±0.02	0.52±0.02	7.69±1.36	1.09±0.02	26.92±0.64
F8	175.6±2.04	0.47±0.02	0.51±0.03	7.84±2.22	1.09±0.03	28.38±0.97
F9	163.3±3.02	0.48±0.03	0.53±0.02	9.43±1.45	1.11±0.02	27.78±1.11

**All values are means, n=3*

Table 3.3.2.1.1: Micromeritic properties of the microsphere of formulation F1-F9

3.3.2.2. Percentage yield, drug entrapment and In vitro buoyancy efficiency of floating microspheres

Formulation code	Percentage yield (% w/w)	Drug entrapment efficiency(%w/w)	In vitro buoyancy (%)
F1	76.84±0.005	76.47±0.956	85.72±1.23
F2	79.50±0.008	72.99±0.789	81.14±1.34
F3	83.54±0.002	70.49±0.743	78.3±1.89
F4	79.83±0.005	84.45±0.568	80.03±2.34
F5	82.68±0.012	81.42±0.973	76.9±3.67
F6	88.9±0.004	80.46±1.041	74.54±3.42
F7	83.66±0.021	90.43±1.023	71.18±1.06
F8	89.37±0.006	85.11±0.897	70.84±1.27
F9	93.77±0.023	82.12±0.539	67.12±1.62

Table 3.3.2.2.1: Percentage yield, drug entrapment and in vitro buoyancy efficiency of floating microspheres

3.3.2.3. In vitro drug release of floating microspheres

In vitro drug release of all formulations varied from 67.14% to 83.69% where F1 had low and F9 had high drug release which shows that as polymer conc. and stirring speed increases; *in vitro* drug release is also increases and HPMC is hydrophilic polymer and F9 has highest conc. of HPMC K15M therefore F9 has highest drug release.

Time	**In vitro %Drug release of Floating microspheres (mean± SD), n=3**								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
1	9.335±0.98	10.090±0.79	10.090±1.23	10.392±1.01	10.694±0.93	10.694±0.89	10.090±0.64	11.599±0.67	12.203±0.89
2	15.988±0.78	15.083±0.72	15.234±1.04	15.536±1.45	16.141±1.05	16.443±1.32	15.536±1.17	15.840±1.12	16.293±1.21
3	21.290±0.56	19.780±0.89	19.026±0.75	20.687±1.03	21.14±0.78	23.708±0.85	22.348±1.23	23.708±1.12	23.710±1.20
4	27.051±0.87	25.691±1.02	24.029±0.76	25.390±0.89	28.562±0.56	30.377±1.04	29.015±1.34	30.378±1.26	30.681±1.21
5	30.705±0.99	29.644±1.32	31.907±1.01	30.703±1.06	30.708±1.48	37.054±1.23	32.973±1.04	37.055±1.54	35.546±1.32
6	35.570±1.21	36.169±1.89	37.075±1.18	37.531±2.05	37.838±1.32	43.889±1.56	42.521±2.08	42.531±1.05	40.870±1.65
7	40.592±1.25	42.249±2.23	43.910±1.08	45.574±1.03	42.711±2.32	48.165±2.65	46.645±1.23	47.258±1.76	48.615±1.48
8	45.921±1.02	46.523±0.89	47.885±0.67	50.305±0.99	46.986±1.58	55.768±1.34	53.944±2.89	55.766±1.23	57.728±1.26
9	48.689±2.03	51.557±0.79	54.430±1.06	57.457±2.08	54.134±2.17	62.322±0.49	61.099±1.23	63.074±1.21	63.227±1.19
10	57.802±2.04	59.163±0.78	61.133±0.99	61.748±1.29	60.837±1.21	67.675±1.13	67.055±1.16	68.730±1.19	69.638±1.12
11	61.791±0.89	63.305±1.17	66.032±1.2	67.553±1.23	69.208±1.34	76.053±1.25	74.829±1.02	76.053±1.08	76.81±1.14
12	67.144±1.24	69.414±1.19	73.352±1.23	76.083±1.17	78.343±1.67	81.573±1.29	80.649±1.12	82.026±1.06	83.690±1.25

Table 3.3.2.3.1: Percentage of Drug release (mean ±SD), n=3 of formulation F_1 to F_9

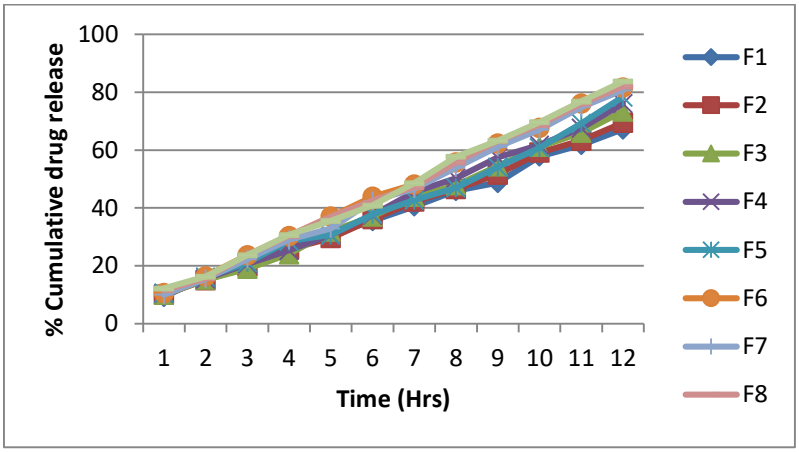


Fig. 3.3.2.3.1: Plot of % cumulative drug release vs. Time for formulations F_1 to F_9

3.3.2.4. Release Kinetics of *in-vitro* drug release

Drug release kinetics studies data for all batches were studied; this data was treated to study the best linear fit model.

1) $Q_1=Q_0+K_0t$ (Zero order kinetics)
2) Log $Q_1=Q_0+K_1t/2.303$ (First order kinetics)
3) $Q_1=K_H\ t^{1/2}$ (Higuchi Model)
4) $Q_0^{1/3}-Qt^{1/3}=K_1t$ (Hixson-Crowell model)
5) $Q_t/Q_\infty=Kt^n$ (Korsemeyer peppas model)

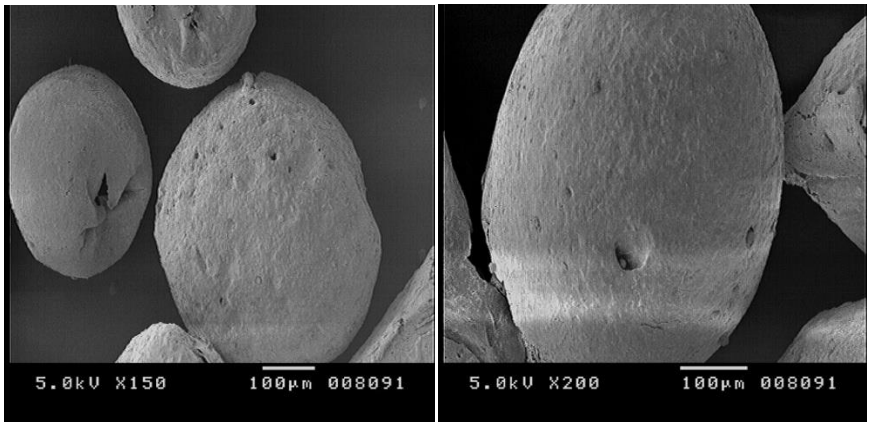
Where,
Q_t=Amount of drug permeated at time t,
Q_0=Initial amount of drug,
K= permeation rate constant
n= release exponent, indicative of drug permeation mechanism.
As observed from kinetics of *in-vitro* drug release data formulations F2, F3, F4, F5, F7, F8 and F9 shows zero order as best fit model and remaining F1 and F6 batches follows Korsmeyer-peppas model.
Most of the formulation followed the zero order equation with n values more than 0.5 thus indicating that the release of the Metoclopramide hydrochloride microspheres is following anomalous transport (non-fickian diffusion) type of release.

Formu-lation code	R value					Best fit model	Parameters for Korsemeyer Peppas equation	
	Zero order	First order	Matrix	Peppas	Hixson Crowell		K	N
F1	0.9916	0.9871	0.9553	0.9982	0.9941	Peppas	9.0972	0.7838
F2	0.9959	0.9839	0.9465	0.9947	0.9934	Zero order	8.9226	0.7988
F3	0.9975	0.9762	0.9386	0.9922	0.9896	Zero order	8.6923	0.8272
F4	0.9972	0.9717	0.9382	0.9928	0.9875	Zero order	9.0009	0.8248
F5	0.9941	0.9524	0.9352	0.9922	0.9754	Zero order	9.4755	0.7970
F6	0.9967	0.9684	0.9471	0.9979	0.9882	Peppas	9.7850	0.8380
F7	0.9982	0.9648	0.9383	0.9965	0.9851	Zero order	9.0501	0.8603
F8	0.9968	0.9657	0.9444	0.9944	0.9863	Zero order	10.0372	0.8240
F9	0.9969	0.9589	0.9408	0.9918	0.9826	Zero order	10.3023	0.8142

Table 3.3.2.4.1: Release Kinetics of *in-vitro* drug release of all formulation

3.3.2.5. SEM study of Metoclopramide hydrochloride floating microspheres

The morphology of microspheres was examined using SEM. The view of the microspheres showed a spherical structure with pore on surface of floating microspheres and a smooth surface morphology



(a) **(b)**

Fig 3.3.2.5.1: SEM photogr aphs of floating microspher
a:SEM of best formulation b:Spherical nature of best fomulation

3.3.2.6. Stability studies

Batch F7 was subjected to stability studies for a period of one month's ($40^0C\pm 2^0C$ and 75%± 5% RH). The stability data of formulation F7 is presented.Physical appearance of the microspheres was same as initial condition. The drug content of the microspheres after storage for one month was within limits. Weights of microspheres were increased compared to initial weight. It may be due to moisture uptake from the storage environment.

Parameter	Initial	1 month
Appearance	Off-white	Off-white
Weight	50 mg	50.25mg
Drug content	99.06%	98.96%

Table 3.3.2.6.1: Stability evaluation of floating microspheres ($40^0C \pm 2^0C$ and 75% ± 5% RH).

3.3.2.7.Multiple regression analysis for 3^2 factorial designs

Table14 shows the statistical evaluation and multiple regression analysis of 3^2 factorial batches for three responses along with their derived factorial equation. The surface plot for the response Y_1 (DEE) indicates that DEE increased as polymer conc. increase and stirring speed increased Fig.11 show the response surface plots for Y_2 (in vitro buoyancy at pH 1.2), indicates that in vitro buoyancy was dependent on both the independent variables, in vitro buoyancy was increased as both the independent variables decreased. Fig.12 shows the surface response plot Y_3 (in vitro drug release) which indicates that the in vitro drug release increased with increase in both independent variable i.e. ratio of HPMC K15M:Eudragit S100 and stirring speed and combined effect X_1X_2 and X_1^2.

Source	Degree of freedom	Sum square	Mean square	F-value	Prob>F
$Y_{1=}$ drug entrapment efficiency					
Model	2	292.70	146.35	46.12	0.0002
X_1	1	237.01	237.01	74.70	0.0001
X_2	1	55.69	55.69	17.55	0.0058
	R^2=0.9389	Adj R^2=0.9186	PredR^2=0.8689	SD=1.78	CV=2.21
Equation	$Y_1=80.44+6.29X_1-3.05X_2$				
Y_2=In vitro buoyancy					
Model	2	265.78	132.89	79.00	<0.0001
X_1	1	216.24	216.24	128.55	<0.0001
X_2	1	49.54	49.54	29.45	0.0016
	R^2=0.9634	Adj R^2=0.9512	Pred R^2=0.9059	SD=1.30	CV=1.70
Equation	$Y_2= 76.23-6.00X_1-2.87X_2$				
Y_3=In vitro drug release					
Model	5	274.41	54.88	405.78	0.0002
X_1	1	221.89	221.89	1637.66	<0.0001
X_2	1	36.18	36.18	267.52	0.0005
X_1X_2	1	2.51	2.51	18.54	0.0231
X_1^2	1	13.75	13.75	101.67	0.0021
X_2^2	1	0.48	0.48	3.53	0.1570
	R^2=0.9985	Adj R^2=0.9961	Pred R^2=0.9820	SD=0.37	CV=0.48
Equation	$Y_3= 78.34+6.08\ X_1+2.46\ X_2-0.79\ X_1X_2-2.62\ X_1^2+0.49\ X_2^2$				

Table 3.3.2.7.1: Multiple regression analysis for 3^2 factorial designs

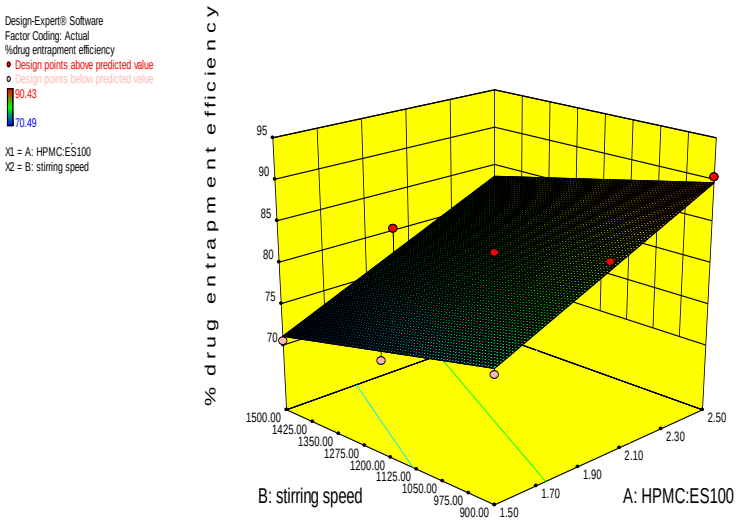


Fig3.3.2.7.1: Response Surface Plot showing effect of variables on drug entrapment efficiency at t_{12}Hr of floating microspheres.

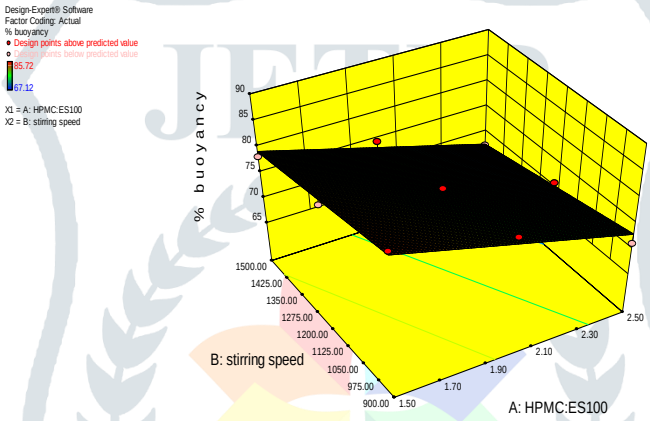


Fig. 3.3.2.7.2: Response Surface Plot showing effect of variables on in vitro buoyancy of floating microspheres

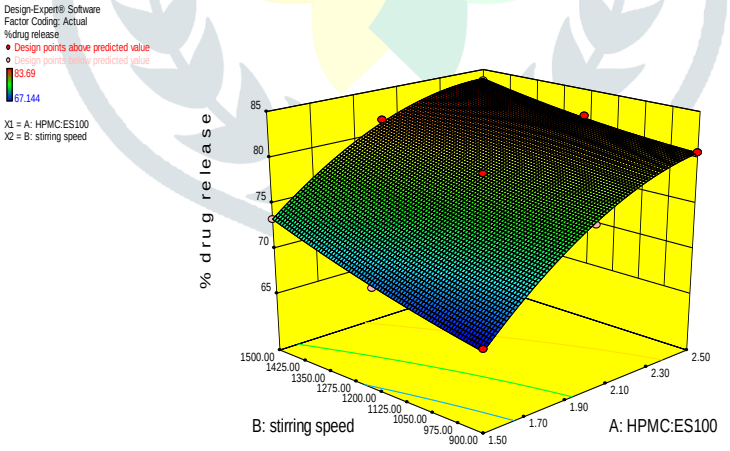


Fig. 3.3.2.7.3: Response Surface Plot showing effect of variables on in vitro drug release of floating microspheres

3.3.2.8. Optimization

It was desirable that the optimized formulation should exhibit maximum drug release, in vitro buoyancy and drug entrapment efficiency. On this basis of analysis by design expert software F7 was selected as the optimized formulation yielding desirability factor of 0.647 . The optimized formulation exhibited % drug entrapment efficiency of 88.82%, 73.99% of in vitro buoyancy after 12 hr and 80.31% drug release.

Constraints:

Name	Goal	Lower Limit	Upper Limit

Ratio of HPMC K15M:Eudragit S100	In range	3:2	5:2
Stirring speed	In range	900	1500
% Drug entrapment efficiency(%w/w)	Target:90.43	70.49	90.43
In vitro buoyancy (%)	Target:85.72	67.12	85.72
In vitro drug release (%)	Target:83.69	67.144	83.69

Table 3.3.2.8.1: Constraints for optimization as per Design Expert Software

Solution:

No.	Ratio of HPMC K15M:ES100	Stirring speed	% Drug entrapment efficiency(%w/w)	In vitro buoyancy (%)	In vitro drug release (%)
1	2.42	900	88.82	73.99	80.31

Table 3.3.2.8.2: Solution for optimization as per Design Expert Software

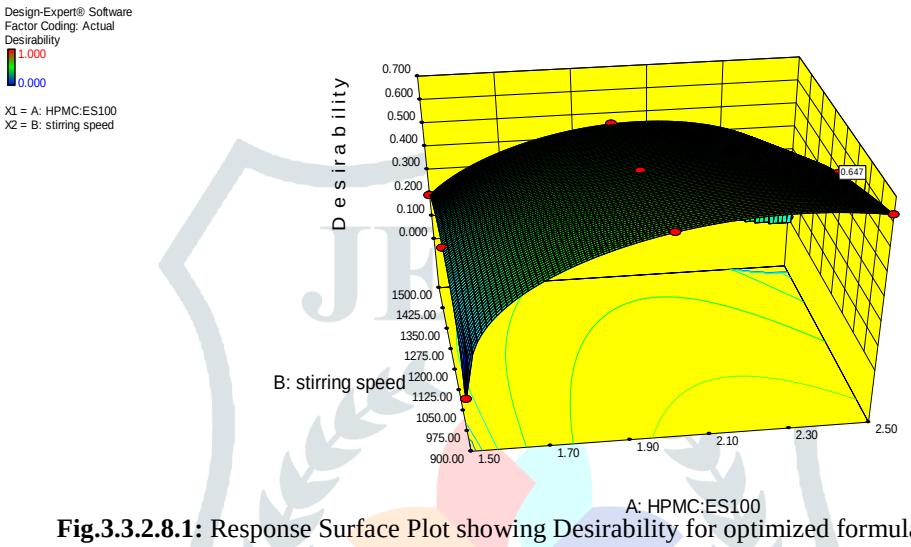


Fig.3.3.2.8.1: Response Surface Plot showing Desirability for optimized formulation

From the solution for optimization as per Design Expert Software it can be concluded as **F7 formulation** is the best formulation with desirability factor **0.647.**

IV. Conclusion

Drug entrapment efficiency is increases at high polymer concentration and low stirring speed and in vitro buoyancy is increased at low rpm and stirring speed. The optimized formulation shows 80% drug release over 12 hrs On this basis of analysis by design expert software F7 was selected as the optimized formulation yielding desirability factor of 0.647. The optimized formulation exhibited % drug entrapment efficiency of 88.82%, 73.99% of in vitro buoyancy after 12 hr and 80.31% drug release.

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