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Formulation And Evaluation Of Floating Microcapsules Of Anti-Parkinson's Disease Drug: Safinamide Mesylate.

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ABSTRACT: Parkinson's disease (PD) is a neurodegenerative disease caused by a complex interaction of loss of dopaminergic and non-dopaminergic neurotransmitter systems. Drugs acting on the dopaminergic pathways are the mainstay of treatment for motor symptoms today. Safinamide (NW-1015) is a novel drug with multiple actions. It is a monoamine oxidase B inhibitor and improves dopaminergic transmission. In addition, it has antiglutamatergic effects and can thus reduce dyskinesias, which is a side effect limiting most dopaminergic therapy. In Phase III trials, safinamide has been found to be a useful adjunctive to dopamine agonists in early PD and has been shown to increase time without increasing troublesome dyskinesias when used as an adjunct to levodopa in patients with advanced PD. A possible neuroprotective role in inhibiting PD disease progression is envisaged and warrants future studies.

Keywords: Parkinson's disease; antiglutamatergic; monoamine oxidase B inhibitor.

I. INTRODUCTION:

Safinamidemesylate (SAF) is an orally availablederivativefromchemical class of á . amino amides,withmultiplemechanismsofactioninvolvingi nhibitionof MAO-B and Dopamine reuptake used in thetreatment of epilepsy and Parkinson.sdisease.Chemically, Safinamidemesylate is, (S)-(+)-2-[4-(3-fluorobenzyloxybenzylamino) propanamide]methanesulfonate(1:1 salt).The chemical structure is shown in Figure 1.**[1, 2]** Previous studies on the solubility of SAF and related salts have been conducted using the excessive powder dissolution method.

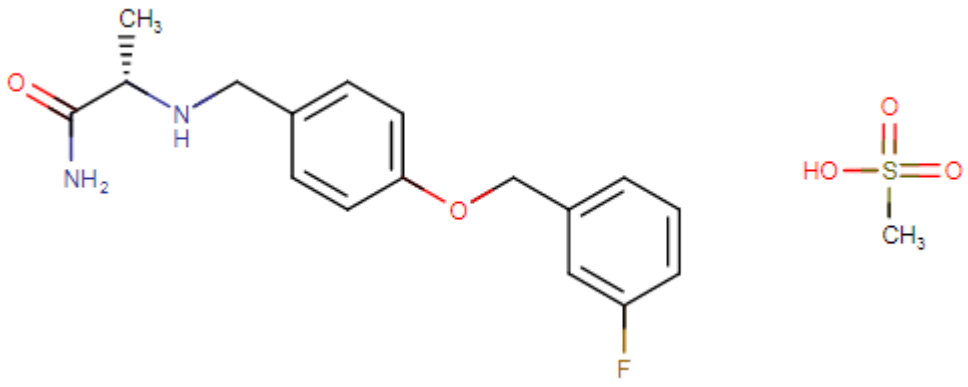

Figure 1: Chemical structure of SafinamideMesylate.

Literature survey reveals a validated chiral liquid chromatographic method for the enantiomeric separation ofsafinamidemesylate [3] and bioassay of safinamide in biological fluids of humans and various animal species [4].

Except this, so far no analytical method was available forestimation of SAF as indicated by detail literature survey.The therapeutic effectiveness and less methods available forits estimation encourage us to undertake this work, so thatquantitative estimation of SAF can be done and

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hence can beused for routine analysis of bulk and formulation as well.

The antiparkinson mechanism of safinamide is through reversible inhibition of selective MAO-B, as a mesylate salt, thus reducing the degradation of dopamine.

It inhibits glutamate release and dopamine reuptake in the brain.Safinamide also blocks sodium and calcium channels, although the clinical significance of this to PD is unknown.

MICROENCAPSULATION

It is a process by which very tiny droplets or particles of liquid or solid material are surrounded or coated with a continuous film of polymeric material.

The product obtained by this process is called as Microcapsules Fundamental Consideration

Generally micro particles consist of two components

1] Core material.

2] Coat or wall or shell material

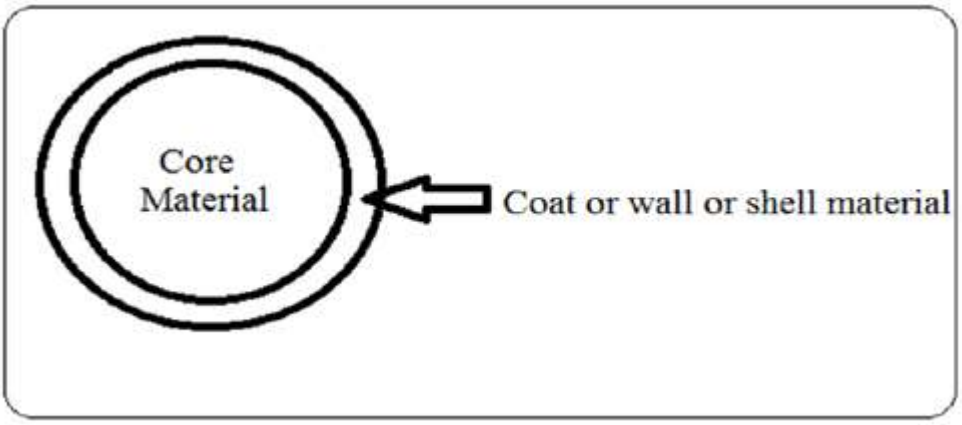

Figure 4: Microcapsules

Core-Material

The material to be coated. It may be liquid or solid or gas. Liquid core may be dissolved or dispersed material.

Composition of core material:

- Drug or active constituent
- Additive like diluents
- Stabilizers

Coating Material

Inert substance which coats on core with desired thickness.

Composition of coating

- Inert polymer
- Plasticizer
- Coloring agent
- Resins,waxes and lipids
- Release rate enhancers or retardants

POLYMER PROFILE/ EXCIPIENTS PROFILE

HPMC- Hydroxy propyl methyl cellulose
EC: Ethyl Cellulose
DCM: Dichloro methane
IPA: Isopropyl Alcohol
Tween 80.

Hydroxypropylmethylcellulose [HPMC]—

Hydroxy propyl methyl cellulose can be used in the development of different drug delivery technology. Nowadays it is a widely used polymer and different viscosity grade of this polymer is available. The hydrophilic and hydrophobic form (both variants) of this polymer is also available. This study includes a review of this polymer on use in different drug delivery system mosty focusing on more recent developments.Hydroxypropyl methylcellulose is an odorless and tasteless, white to slightly off-white, fibrous or granular, free-flowing powder that is a synthetic modification of the natural polymer, cellulose. Specifically, it is a modification of alkali

cellulose, which is produced when purified wood pulp is treated with 18% sodium hydroxide solution. Methyl and hydroxypropyl ether groups are introduced into the molecule by reacting the alkali cellulose with methyl chloride and propylene oxide, respectively. The degree of substitution (DS) of commercial HPMC with these methoxy and hydroxypropoxy groups will vary depending on the commercial use and properties desired. These added groups confer on the molecule its unique

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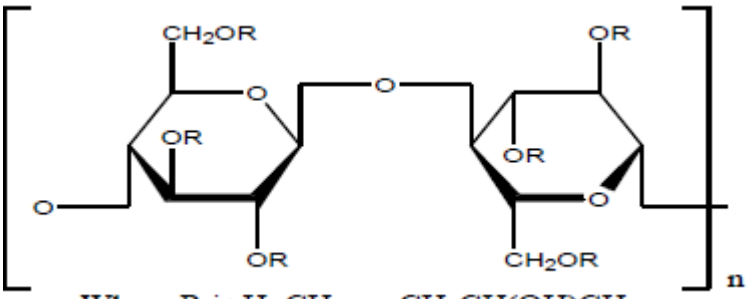
properties of being cold-water soluble, while at the same time exhibiting reversible gelation when heated and recooled.

The reason for its widespread acceptance include -
(1) solubility characteristics of the polymer in gastrointestinal fluid, and in organic and aqueous solvent-systems,
(2) noninterference with tablet disintegration and drug availability,
(3) flexibility, chip resistance and absence of taste and odor,
(4) stability in the presence of heat, light, air or reasonable levels of moisture,
(5) ability to incorporate color and other additives into the film without difficulty. The
interaction of this polymer with colorants is rare.

HYDROXPROPYL METHYL CELLULOSE
Synonym :Methocel, Hypromellose, Hypromellosum
Chemical name: Cellulose -2 hydroxypropyl methyl ether
Empirical formula: o-methylated and 0 – (2-hydroxpropylated) Cellulose.
Molecular weight: 10,000 – 1,500,000



Where R is H, CH_3, or $CH_3CH(OH)CH_2$

Functional category: Coating agent, film former, rate controlling polymer for sustained release, stabilizing agent, suspending agent, tablet binder, viscosity increasing agent.
Application in pharmaceutical formulation and technology:
Hypermellose is primarily used as a tablet binder (2% - 5% w/w concentration), film coating (2% - 20% w/w concentration), and as extended release matrix (10 – 80% w/w in formulation). Hypermellose is used as a suspending and thickening agent in topical formulation, particular ophthalmic preparation (0.45 – 1.0% w/w).
Hypermellose is also used as an emulsifier, suspending agent and stabilizing agent in -topical gels and ointments. In addition hypromellose is used in the manufacture, as an adhesion in plastic bandages and as a wetting agent for hard contact lenses. It is also added is cosmetic and food products.
Description: Odourless, tasteless, white (or) creamy white fibrous (or) granular powder.
Pharmaceutical specification:
pH : 5.5 – 8.0 (1% w/w solution)
Melting point: 1900 – 2000c.
Moisture content: Hypermellose absorbs moisture from the atmosphere.
Specific gravity: 1- 26
Solubility: Soluble in cold water, forming a viscous colloidal solution.
Insoluble in chloroform, ethanol and ether, but soluble in mixture of ethanol and dichloromethane, mixture of methanol and dichloro methane.
Viscosity: A code range of viscosity types are commercial available in (2% w/v) of aqueous solution.

Stability and storage conditions:
Hypermellose powder is a stable material although it is hygroscopic after drying.
Solutions are stable at pH – 3-11. Aqueous solutions are comparatively enzyme resistant providing good viscosity stability during long-term storage. Hypermellose powder should be stored in a well closed contains in a cool, dry place.

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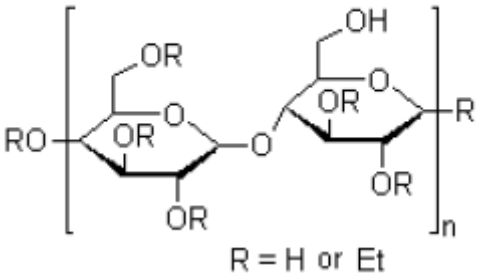
Table 9: Different viscosity grades of Hypermellose:

HYPERMELLOSE GRADE	VISCOSITY (MPAS)
K 100 LVP	80 – 120
K 4 M	3000 – 5600
K 15 MP	12000 – 21000
K 100 MP	80000 – 120000
E 4 MP	3500 – 5600
E 10 MPCR	8000 – 13000
E 3 PREM LV	2.4 – 3.6
E 5 PREM LV	4 – 6
E 6 PREM LV	5 – 7
E 15 PREM LV	12 – 18
E 50 PREM LV	40 – 60
K 3PREM LV	2.4 - 3.6

ETHYL CELLULOSE
Name: Ethyl cellulose
CAS No.: 9004-57-3

Molecular Structure:



Formula: Unspecified
Deleted CAS: 11097-03-3,154608-92-1,166735-68-8,51331-16-9,57307-96-7
Synonyms: STD 7;Aquacoat ECD 30FMC;EC (Ethyl cellulose);MFA-EM;N 50 (polysaccharide);Cellulose ethyl;N 22 (cellulose derivative);Ethocel N7;Ethocel 150;G 200 (polysaccharide);T 100;G 200;Triethyl cellulose;Cellulose, triethylether;N 200 (cellulose derivative);N 22G;Aquacoat;Ethocel MED;Aquacoat ECD 30;Surelease;K 5000;Aqualon NF;Ethocel;Ethocel E7;MED 20;N 4 (cellulose derivative);Ethocel N200;G 50 (Polysaccharide);Hercules T;Cellulose, ethyl ether;Ethocel E50;SPT 50 cps;Ethocel STD;N 14 (cellulose derivative);ETs;T 100 (Polysaccharide);Ampacet E/C;X 62-9201A;SPT 50CPS;N 5;ET 100 (cellulose derivative);Nixon E/C;Ethocel 890;Cellulose ethyl ether;Ethyl Cellulose 70CPS;
Appearance:
White powder

ETHYL CELLULOSE-[7cps]
EC is a derivative of cellulose in which some of the hydroxyl groups on the repeating
anhydroglucose units are modified into ethyl ether groups,largely called as non-ionic ethyl ether of cellulose(Fig. 1) (3).EC has extensively been used for microencapsulation
due to its many versatile properties such as

1. White to light tan odorless and tasteless powder or granular substance;

melting point range 240n2558C; specific density range 1.07n1.18 with 135n1558C heat distortion point and 330n3608C fire point;

2. water insoluble but soluble in many organic solvents such as alcohol, ether, ketone and ester; biocompatible and compatible with many celluloses,resin and almost all plasticizers;

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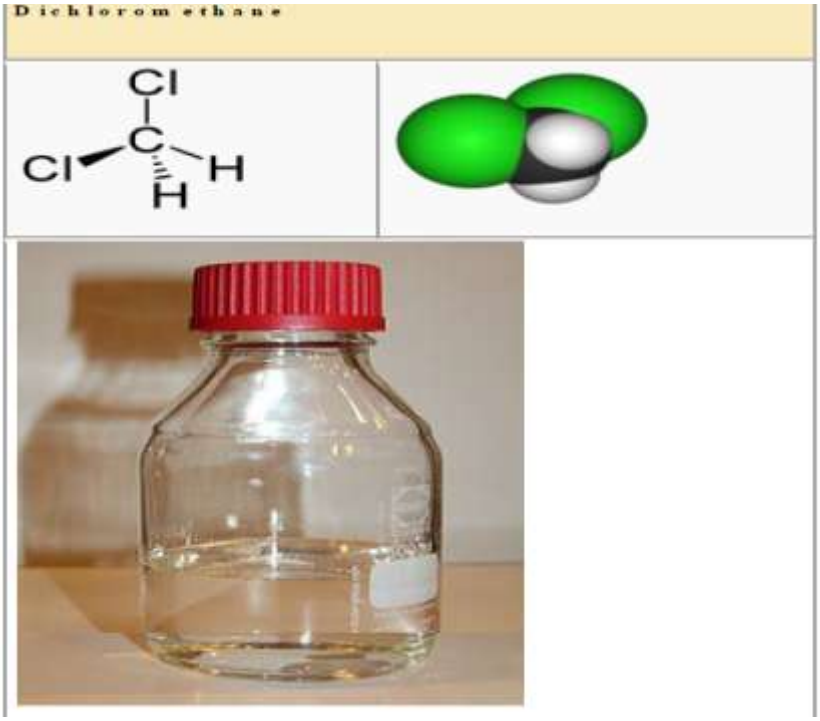
3. Nonbiodegradable,thus used in oral formulation only;
4. stable against light, heat, oxygen and wetness and chemicals;
5. non-toxic; non-irritant;
6. Tablet binder to impart plastic flow properties to particles; ability to absorb pressure and hence protect the coating from fracture during compression. Its thinfilm exhibits good flexibility and mechanical strength in a wide range of temperature.

DICHLOROMETHANE-

Dichloromethane From Wikipedia, the free encyclopedia



IUPAC name : Dichloromethane

Other names :Methylene chloride, methylene dichloride, Solmethine, Narkotil, Solaesthin, Di-clo, Freon 30,

R-30, DCM, UN 1593, MDC	
Identifiers	
CAS number	75-09-2
PubChem	6344
ChemSpider	6104
UNII	588X2YUY0A
EC number	200-838-9
KEGG	D02330
ChEBI	CHEBI:15767
ChEMBL	CHEMBL45967
RTECS number	PA8050000
Jmol-3D images	Image 1

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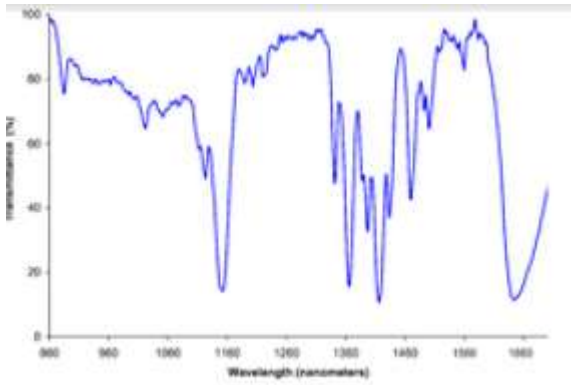
Properties	
Molecular formula	CH2Cl2
Molar mass	84.93 g/mol
Appearance	Colorless liquid
Density	1.33 g/cm3, liquid
Melting point	-96.7 °C, 176 K, -142 °F
Boiling point	39.6 °C, 313 K, 103 °F
Solubility in water	13 g/L at 20 °C
Vapor pressure	47 kPa at 20 °C

Hazards	
MSDS	External MSDS
R-phrases	R40
S-phrases	S23 S24/25 S36/37
Main hazards	Harmful (Xn), Carc. Cat. 2B
NFPA 704	1 2 0
Flash point	None
Autoignition temperature	556 °C

Supplementary data page	
Structure and properties	n, er, etc.
Thermodynamic data	Phase behaviour Solid, liquid, gas
Spectral data	UV, IR, NMR, MS
(verify) (what is: /?) Except where noted otherwise, data are given for materials in their standard state (at 25 °C, 100 kPa)	
Infobox references	



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Near IR absorption spectrum of dichloromethane showing complicated overlapping overtones of mid IR absorption features.

Dichloromethane (DCM)—or methylene chloride—is an organic compound with the formula CH2Cl2. This colorless, volatile liquid with a moderately sweet aroma is widely used as a solvent. Although it is not miscible with water, it is miscible with many organic solvents.[1]

Isopropyl Alcohol

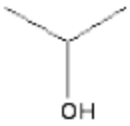
Formula: C3H8O

Molecular weight: 60.0950

IUPAC Standard InChI: InChI=1S/C3H8O/c1-3(2)4/h3-4H,1-2H3

IUPAC Standard InChIKey: KFZMGEQAYNSKOFK-UHFFFAOYSA-N

CAS Registry Number: 67-63-0



Chemical structure

Other names: 2-Propanol; sec-Propyl Alcohol; Alcojel; Alcosolve 2; Avantin; Avantine; Combi-Schutz; Dimethylcarbinol; Hartosol; Imsol A; Isohol; Isopropanol; Lutosol; Petrohol; Propol; PRO; Takineocol; 1-Methylethyl Alcohol; iso-C3H7OH; 2-Hydroxypropane; Propane, 2-hydroxy-; sec-Propanol; Propan-2-ol; i-Propylalkohol; Alcolo; Alcoolisopropilico; Alcoolisopropylique; Alkolave; Arquad DMCB; iso-Propylalkohol; Isopropyl alcohol, rubbing; IPA; Lavacol; Visco 1152; Alcosolve; i-Propanol; 2-Propyl alcohol; Spectrar; Sterisol hand disinfectant; UN 1219; n-Propan-2-ol; 1-methylethanol; Propanol-2; Virahol; IPS 1

TWEEN-8018:

1. Nonproprietary Names:

BP: Polysorbate 80

JP: Polysorbate 80

PhEur: Polysorbate 80

USP-NF: Polysorbate 80

Tween80_molecule

2. Synonyms:

Polysorbate 80 Atlas E; Armotan PMO 20; Capmul POE-O; Cremophor PS 80; Crillet 4; Crillet 50; Drewmulse POE-SMO;Montanox80;Tween 80.

3. Chemical Names and CAS Registry Numbers:

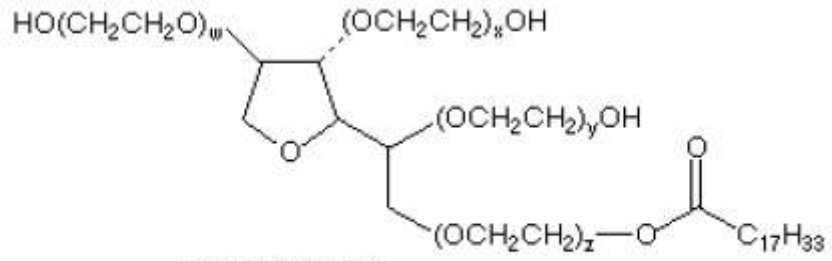
Polysorbate 80 Polyoxyethylene 20 sorbitanmonooleate (9005-65-6)

4. Empirical Formula and Molecular Weight: C64H124O26, Mol. wt: 1310

5. Functional Category:

Dispersing agent; emulsifying agent; nonionic surfactant; solubilizing agent; suspending agent; wetting agent.

FIG 4.2: STRUCTURE OF TWEEN-80



Polysorbate 80
(Sum of w, x, y, and z is 20)

6. Description:

Polysorbates have a characteristic odor and a warm, somewhat bitter taste. Their colors and physical forms at 2580C , although it should be noted that the absolute color intensity of the products may vary from batch to batch and from manufacturer to manufacturer.

7. Incompatibilities:

Discoloration and/or precipitation occur with various substances, especially phenols, tannins, tars, and tarlike materials. The antimicrobial activity of paraben preservatives is reduced in thepresence of polysorbates.

8. Stability and Storage Conditions:

Polysorbates are stable to electrolytes and weak acids and bases; gradual saponification occurs with strong acids and bases. The oleic acid

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esters are sensitive to oxidation. Polysorbates are hygroscopic and should be examined for water content prior to use and dried if necessary. Also, in common with other polyoxyethylene surfactants, prolonged storage can lead to the formation of peroxides. Polysorbates should be stored in a well-closed container, protected from light, in a cool, dry place.

9. Applications in Pharmaceutical Formulation or Technology

Polysorbates containing 20 units of oxyethylene are hydrophilic nonionic surfactants that are used widely as emulsifying agents in the preparation of stable oil-in-water pharmaceutical emulsions. They may also be used as solubilizing agents for a variety of substances including essential oils and oil-soluble vitamins, and as wetting agents in the formulation of oral and parenteral suspensions. They have been found to be useful in improving the oral bioavailability of drug molecules that are substrates for P-glycoprotein.

II. MATERIALS

Sr.No	Drug/ Excipient/ Polymer/ Solvent	Manufacturer
1	Safinamide (SAF)	Sun Pharma, Mumbai.
2	Hydroxy propyl methyl cellulose (HPMC 5cps	S. D. Fine Chemicals
3	Ethyl cellulose 7cps	S. D. Fine Chemicals
4	Dichloromethane	S. D. Fine Chemicals.
5	Isopropyl alcohol	S. D. Fine Chemicals.
6	Tween 80	Laboratory Grade
7	Hydrochloric acid	Laboratory Grade
8	Sulphuric acid	Laboratory Grade

Table No.1: List of Drug, Excipients / Polymer and Solvent

LIST OF EQUIPMENTS

S. No.	Equipments	Company
1	Glassware	Borosil
2	Stirrer	Remi stirrer(2500rpm)
3	Hot plate	Optics technology(Delhi)
4	Tray dryer	Optics technology(Delhi)
5	Sonicator	PCI-SS
6	Optical microscope	Dalal&co-Chennai
7	UV Spectrophotometer	E2371 spectrophotometer
8	Dissolution apparatus	Campbell electronics(Mumbai)
9	Scanning electron microscope	Hitachi model SU 1500,JEOL JSM T330A scanning microscope(Japan)
10	FTIR 200 spectrometer	Spectrum one Perkin Elmar USA
11	DSC	Toledo DSC Mettler Star SW 9.20

Table No.2: List of equipment's

III. METHOD AND EXPERIMENTAL WORK

EXPERIMENTAL DESIGN AND PROCESS OF OPTIMIZATION

A full 2 factorial design was introduced to optimize the formulation of Safinamide (SAF)loaded EC+ HPMC microcapsules using the solvent evaporation technique (Table 1).

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Entrapment efficiency was considered as a measurable parameter for this study.

DOE APPROACH

EXPERIMENTATION

A design matrix comprising of 8 experimental runs was constructed using DOE Pro XL Software to investigate the effect of four factors .
- Safinamide (SAF)concentration as (A),
- EC concentration as (B),
-HPMC concentration as (C) on the response variable i.e. % entrapment efficiency .

Experimental Design and Process Optimization

A full 2 factorial design was introduced to optimize the formulation of Safinamide loaded EC+ HPMC microcapsules using the solvent evaporation technique .

A design matrix comprising of 8 experimental runs was constructed using DOE Pro XL Software to investigate the effect of 3 factors .
- Safinamide concentration as (A),
- EC concentration as (B),
- HPMC concentration as © on the response variable i.e. % Drug released at 1 hour (D1) and % Drug release at 8 hours (D8) were considered as measurable parameters.

Volume of solvent (50 ml), ratio of IPA and DCM (1:1) , volume of aqueous phase (500 ml) concentration of Tween (2.5ml), stirring speed (500 rpm) and temperature (ambient) were kept constant.

DESIGN OF EXPERIMENT

Formulation	Safinamide	Ethyl cellulose 7cps	HPMC
F1	L	L	L
F2	L	L	H
F3	L	H	L
F4	L	H	H
F5	H	L	L
F6	H	L	H
F7	H	H	L
F8	H	H	H

FORMULATION CHART

Sr. No.	Ingredients	LLL	LLH	LHL	LHH	HLL	HLH	HHL	HHH
1	Safinamide	250	250	250	250	1000	1000	1000	1000
2	Ethyl cellulose	250	250	1000	1000	250	250	1000	1000
3	HPMC 5cps	2	20	2	20	2	20	2	20
4	Isopropyl alcohol (IPA) (ml)	25	25	25	25	25	25	25	25
5	Dichloromethane (DCM) (ml)	25	25	25	25	25	25	25	25
6	Tween 80 (ml)	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
7	Water (ml)	500	500	500	500	500	500	500	500

Safinamide (SAF) POWDER

Colour: White to off-white crystalline powder.

Melting point determination: The melting point of the obtained drug sample was found to be 210°C which is the reported range of 208°C -212 °C.It complies with the USP standards thus indicating the purity of the drug soluble.

Solubility analysis: Safinamide sample was found to be soluble in organic solvent such as ethanol, DMF

Spectral analysis:

Determination of max of Safinamide by using 0.1N Hcl :

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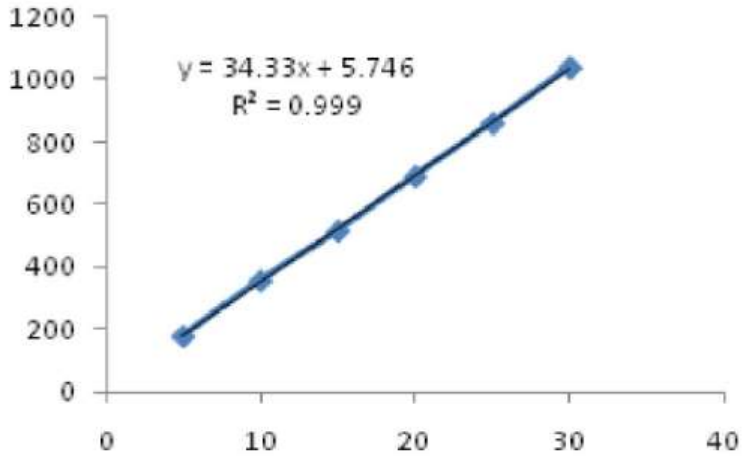
The absorption maximum of Safinamide in 0.1 N Hcl was found to be 278 nm.

Calibration curve values Safinamide in 0.1N Hcl



S.No	Concentration	Absorbance
1	10	0.107
2	20	0.219
3	30	0.332
4	40	0.441
5	50	0.542

IV. RESULTS & DISCUSSION

A total of 3 formulations of Safinamide floating microcapsules were formulated by solvent evaporation technique using DOE approach, which was already discussed in the previous chapter. The formulations were subjected to evaluation parameters like particle size, surface morphology, drug entrapment efficiency, In-vitro drug release studies.

PRE-FORMULATION STUDIES

FT-IR Spectroscopy

The FT-IR spectrum of the pure drug was found to be similar to the standard spectrum of Safinamide. The spectra of the drug and the cross linked microcapsules were shown in the figures 8.1,8.2 respectively. Melting Point Determination .The melting point of the obtained drug sample was found to be 1960C which is the reported range of 208 to 212^{0}C.It complies with the USP standards thus indicating the purity of the drug sample.

Solubility Analysis

Safinamide sample was found to be soluble in water (18.8 mg/ml), 2-propanol and
ethanol, sparingly soluble in acetone. Soluble in 0.1N NaOH .

Compatibility studies

From the FT-IR spectra of the pure drug and the combination spectra of drug with the polymers, it was observed that all the characteristics peaks of Safinamide were present in the combination spectra thus indicating the compatibility of the drug with the polymer used.

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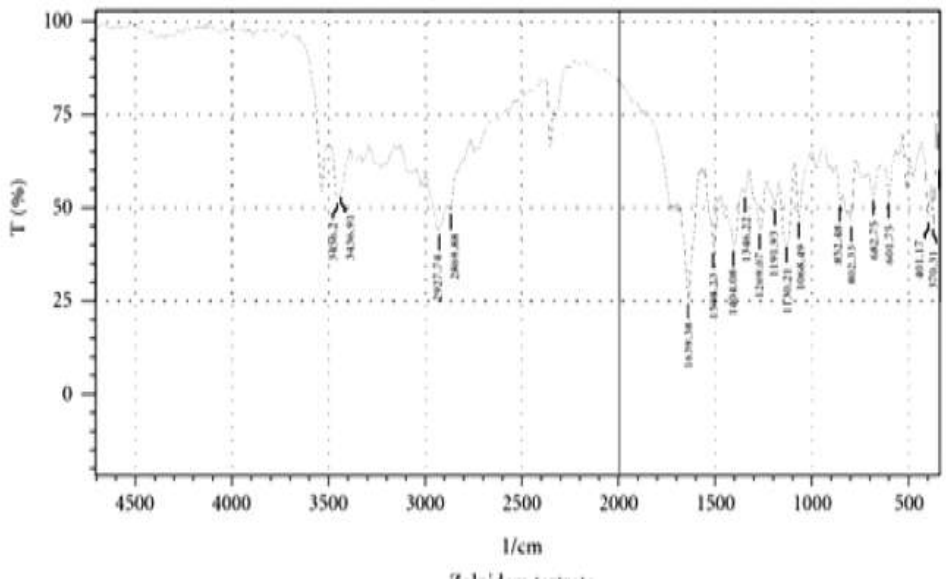
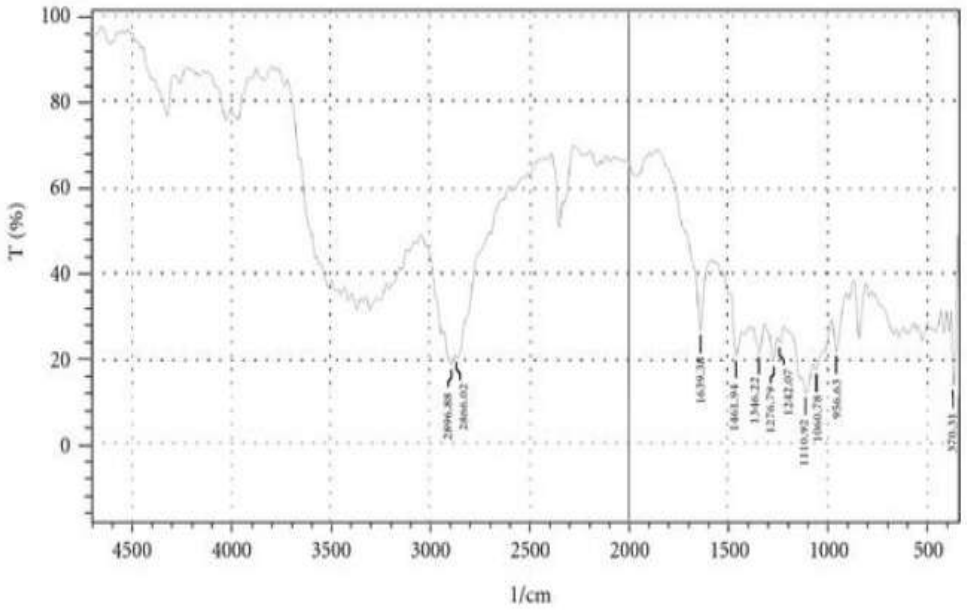


FIG 8.2: FT-IR OF OPTIMIZED FORMULATION.



The FTIR spectrum for the drug loaded microcapsules indicates that there is no chemical interaction between the drug and the polymers used during the process of microencapsulation.

Standard Calibration Curve of Safinamide in Buffers (pH 1.2):

Standard calibrated values of Safinamide in 0.1N HCl were tabulated as follows. They were at different concentrations ranging from 1-5µg/ml in acidic buffer (pH 1.2). The curves of respective values are also presented below.

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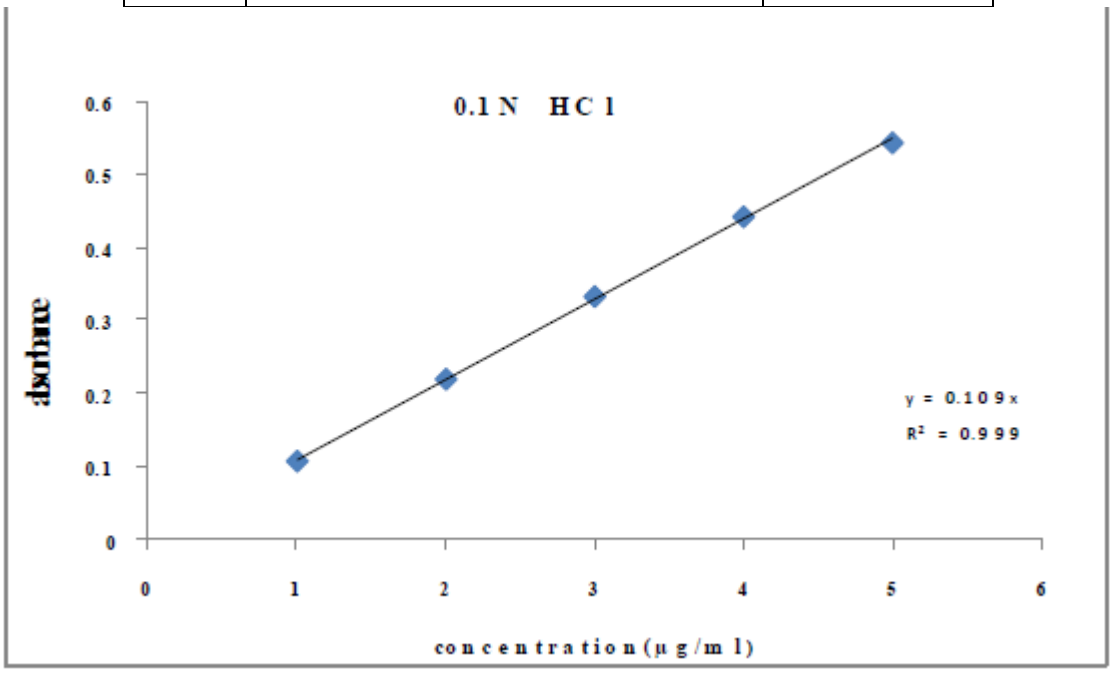
Table 3: Calibration values of Safinamide in 0.1N HCl.

S.NO	CONCENTRATION	ABSORBANCE
1	1	0.107
2	2	0.219
3	3	0.332
4	4	0.441
5	5	0.542



Percentage yield :

Percentage yield of different formulations,F1-F8,were calculated and the yield was found to be above 45%.The results are tabulated in the Table 8.2.the results indicate that the solvent evaporation technique gives excellent yield of the floating microcapsules...

Table 4: Percentage Yield of Formulation

Formulation	Percentage Yield(%w/w)
F1	54.82
F2	59.45
F3	77.92
F4	80.23
F5	46.87
F6	48.57
F7	65.97
F8	68.97

DISCUSSION:

The yield of microcapsules seems to depend on the concentration of polymer in the preparation.

For formulation F3 , F4, F7 and F8, where the EC concentration is 1000 mg, the yields are > 60%.

For formulations with low EC concentration, the yields are in the range of 45 to 55%.

CHARACTERIZATION OF MICROCAPSULES

Particle size analysis

Particle size distribution of microcapsules was determined by optical microscope fitted with an ocular micrometer and stage micrometer. The

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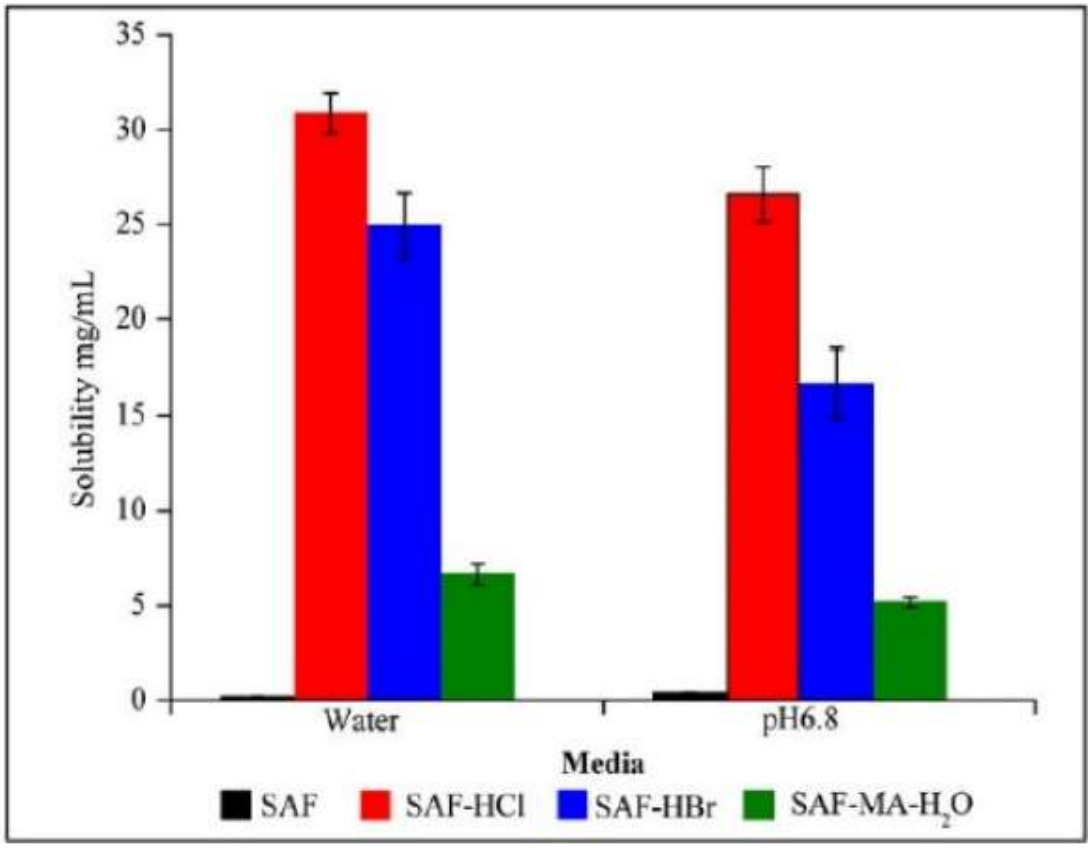
particle sizes of the microcapsules were found in the range of(65-525µm) for 8formulations(DOE).The particle size of the formulations were shown in the table

Table 3. Solubility and intrinsic dissolution rate (IDR) of safinamide and its new salts in water and pH 6.86.

Compound	Aqueous Solubility (mg/mL)	Solubility at pH 6.86 (mg/mL)	IDR in Aqueous Medium ($mg/cm^2/min$)	IDR at pH 6.86 ($mg/cm^2/min$)
SAF	0.19	0.39	0.013	0.024
SAF-HCl	30.86	26.59	4.16	0.14
SAF-HBr	24.93	16.69	6.03	1.49
SAF-MA	Unstable	Unstable	0.67	0.037
SAF-MA-H_2O	6.66	5.18	0.64	0.035



DISCUSSION:

For all formulations, the microcapsules are in the average particle size range of 250 to 375 µm. The particle size distribution is independent of the formulation and is dependent more on the process followed.

Shape and surface morphology

Surface morphology and internal cross sectional structure of the floating microcapsules were investigated with scanning electron microscope.SEM photomicrographs of the blank microcapsules, optimized formulation were shown in the figures. The microcapsules were smooth, spherical and discrete particles. Very less particulate matter of the drug were seen on the surface of the microcapsules indicating uniform distribution of the drug in the polymer network.

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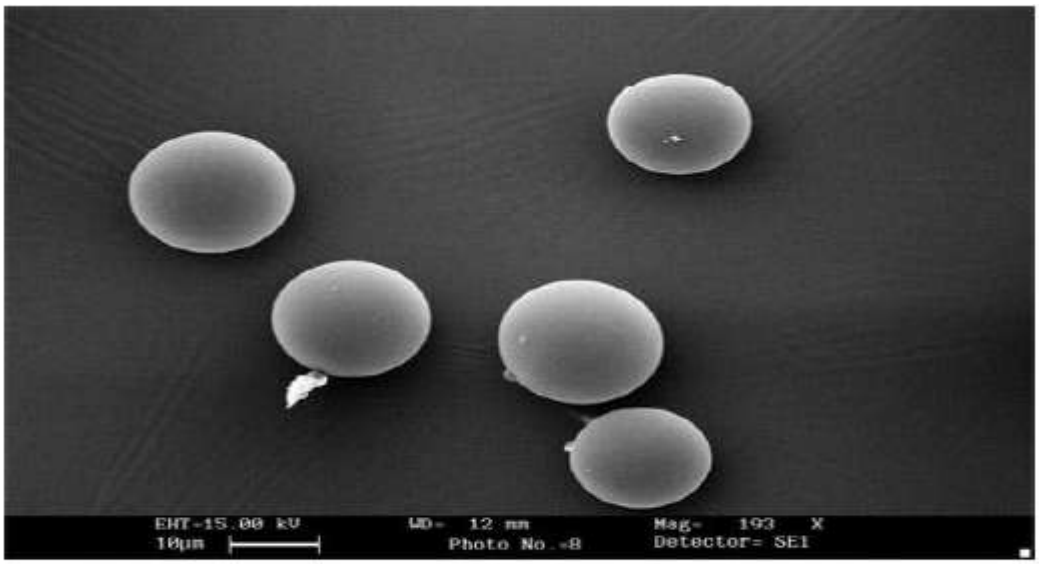

Fig 8.10: SEM of blank microcapsules

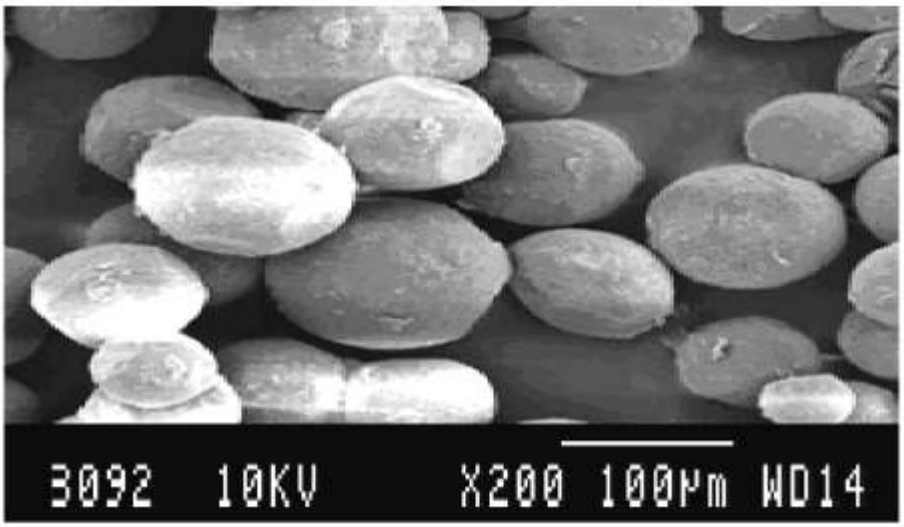

Fig 8.11: SEM of Foptimal

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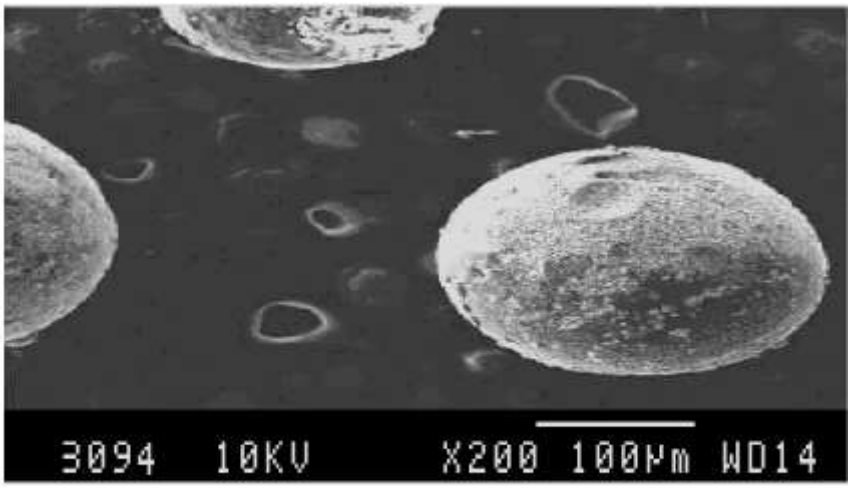

Fig 8.12: SEM of F optim a2

DISCUSSION:

The SEM images show spherical microcapsules with a rough and porous surface. The microcapsules for the scale up batch (Fig 8.12) shows that the microcapsules obtained for the scale up batch are reproducible in surface characteristics.

In-vitro Dissolution Studies:

In vitro release study of Safinamide floating microcapsules were performed in the following pH media (pH 1.2) at 370C ±0.50C.

- In vitro dissolution testing was conducted on microcapsules equivalent to 12.5 mg of Safinamide.
- Microcapsules were filled in hard gelatin capsules shells
- USP Type I apparatus was used
- Media 900 ml 0.1N HCl
- RPM: 50 rpm
- Time points: 0. 0.5, 1, 2, 4 and 8 hours
- Estimation by UV spectrophotometry.

The in vitro release profile of Safinamide Floating microcapsules was shown in

Table 6: Dissolution profile at pH 1.2

TIME		DISSOLUTION PROFILE FOR Safinamide FLOATING MICROCAPSULES						
	LLL	LLH	LHL	LHH	HLL	HLH	HHL	HHH
	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
0.5	6.35	9.23	1.87	3.23	35.87	44.32	4.32	7.54
1	11.87	18.45	3.69	7.89	72.61	89.45	7.29	15.88
2	24.79	42.67	10.44	18.44	88.45	90.76	18.35	33.49
4	45.32	75.34	35.68	43.87	90.26	98.12	38.44	67.7
8	85.29	94.35	65.43	72.64	98.23	98.5	82.48	90.58

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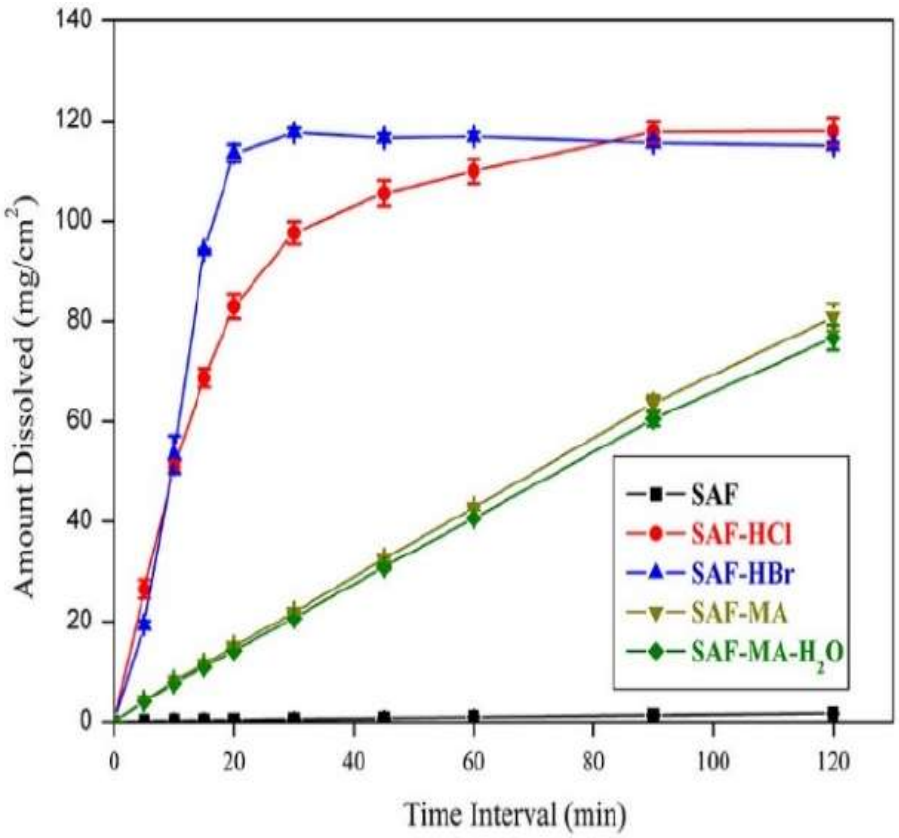

DISCUSSION:

- The drug release rate and extent is dependent of the ratio of the drug and ethyl cellulose as well as the pore former concentration.
- For formulations with Drug to polymer ratio 1:1 (F1, F2, F7, F8), the release is dependent on concentration of HPMC (faster release for higher HPMC levels)
- For formulations with drug to polymer ratio 1:4, F3 and F4 the release is very slow (< 70% in 8 hours)
- For formulations with drug to polymer ratio 4:1, F5 and F6 the release is very fast (> 80% in 2 hours)

Release rate of Safinamide from formulations (F1 to F8)

- In order to understand the mechanism of drug release from the microcapsules, the in vitro drug release data were fitted to Korsmeyer and Peppas release model and interpretation of release exponent values enlightens in understanding the release mechanism from the dosage form. The release exponents thus obtained were from 0.874 to 1.353 for the formulations F1 TO F4 and F7 TO F8.. Based on these values we can say that formulations exhibited super case ii transport.
- The release exponents formulations F6 & F5 was found to be 0.244 & 0.322 Based on these values we can say that formulations exhibited anomalous diffusion mechanism (non fickian transport).
- The formulations F1 & F3 showed higher r values for Korsmeyer and Peppas release plot indicating that the drug release from these formulations exhibited anomalous diffusion mechanism. Also the remaining formulations showed higher r values for first order plot indicating that the drug release followed first order kinetics and also the drug release from the microcapsules were by both diffusion and erosion

Stability Studies

Drug stability is an important index for evaluating drug shelf life. The accelerated stability testsof SAF and all four salts under different humidity conditions (25^{o}C/75%, 25^{o}C /85%, 25^{o}C /97%) were tested for 14 days. The results from the

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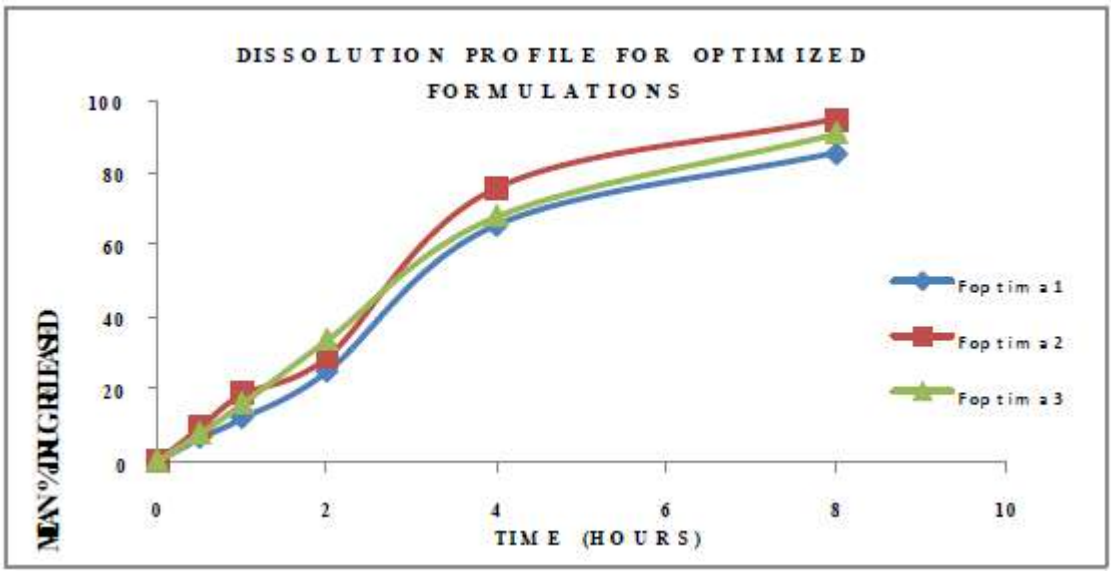
PXRD analysis indicated that all salts except SAF-MA had good stability under the three humidity conditions (Figures S9–S12). However, the SAF-MA salt was not stable at high humidity (Figure S13) and some of this salt transformed to SAF-MA-H2O. The evidence for this was the characteristic peaks at 7.96, 11.16, 15.76 and 16.22_, which were attributed to the SAF-MA-H2O salt

DISCUSSION:

The release of Safinamide at 1 hour and 8 hours' time points were taken as the measurable parameters for running the DOE experiments. The 1 hour time point indicates the rate of release and the 8 hours' time point is a measure the extent of release. The following are the observations from the DOE software output:

(1) For both 1 hour and 8 hours, there is a strong positive interaction between the drug to EC ratio and the rate and extent of drug release.
(2) HPMC 5 cps which is added as the pore former does not show either positive or negative impact on drug release. However, for formulations having HPMC in higher concentrations, the drug release is more complete (at higher EC level) than formulations having low level of HPMC
(3) The design space for the Safinamide, EC and HPMC is defined as per Table 8.6
(4) In order to confirm the design space, 3 formulations within the space were fabricated at a larger scale and evaluated for dissolution profile.
(5) These formulations were subjected to accelerated stability studies after filling into hard gelatin capsules shells.

Dissolution profile for optimized formulation of Safinamide microcapsules:



DISCUSSION:

The dissolution profile for all three formulations fabricated within the design space are showing Matching values. This indicates that any formulation fabricated within the design space will give a product having dissolution profile in a very narrow range of acceptability.

In order to understand the mechanism of drug release from the microcapsules, the in vitro drug release data of the optimized formulations were fitted to Korsmeyer and Peppas release model and interpretation of release exponent values enlightens in understanding the release mechanism from the dosage form. The release exponentsthus obtained were from 0.874, 0.996 and 0.927. Based on these values we can say that formulations exhibited super case II transport All the optimized formulations showed higher r values for first order plot indicating that the drug release followed first order kinetics and also the drug release from microcapsules were by both diffusion and erosion.

ACCELERATED STABILITY STUDIES FOR SAFINAMIDE FLOATING MICROCAPSULES

Three batches of optimized formulations were fabricated as per the table below:

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S.no	Formulation No.	Formulation Ingredients	Mg/unit	Mg/500unit
1	F optima 1	Safinamide	50	25
		EC	145	72.5
		HPMC	0.2	0.1
2	F optima 2	Safinamide	60	30
		EC	147	73.5
		HPMC	1.0	0.5
3	F optima 3	Safinamide	70	35
		EC	150	75
		HPMC	2	1.0
		Tween 80 (ml)		100
		IPA (ml)		500
		DCM (ml)		500
		Water (ml)		5000

The batches were fabricated by the process described in Materials and Methods. The process was reproducible at this scale.

These batches were evaluated for assay, % entrapment efficiency , flow properties and in vitro dissolution profile in 0.1N HCl. The results of the physical properties, assay an d% entrapment efficiency are given in Table. The invitro dissolution profile for these 3 batches is given in Table.

The microcapsules were filled in size =1‘ hard gelatin capsules shells, packed in 90 cc HDPE container and subjected to accelerated stability studies at 40.C/75% RH stability conditions. Samples were withdrawn at 1M, 2M and 3M intervals and evaluated for assay and in vitro dissolution testing. The results are given in Table

Tests	Specifications	F optima1			F2			F3		
		1M	2M	3M	1M	2M	3M	1M	2M	3M
Description	White to off white microcapsules filled in transperant size ‘1’ capsules shells	Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies
Assay (mg/100 mg)	between 20 to 35 mg/100 mg	25.40	24.98	25.00	24.77	24.89	24.64	28.79	27.68	27.54

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Targeted Dissolution profile										
0	0	0	0	0	0	0	0	0	0	0
0.5	NMT 10%	6.00	5.99	6.28	8.76	8.57	8.01	7.54	7.00	7.04
1.0	10–20%	10.97	10.00	11.43	15.88	13.09	15.54	17.28	16.43	15.98
2.0	15–40%	24.78	23.51	27.84	25.32	27.12	28.25	34.08	32.15	35.04
4.0	55–75%	63.37	60.43	65.33	70.66	73.07	71.17	72.91	70.69	71.45
8.0	NLT80 %(Q)	87.98	87.09	88.96	90.42	93.22	95.24	92.83	89.09	93.65

V. SUMMARY & CONCLUSION:

In order to understand the mechanism of drug release from the microcapsules, the in vitro drug release data of the optimized formulations were fitted to Korsmeyer and Peppas release model and interpretation of release exponent values enlightens in understanding the release mechanism from the dosage form. The release exponents thus obtained were from 0.874, 0.996 and 0.927. Based on these values we can say that formulations exhibited super case II transport.All the optimized formulations showed higher r values for first order plot indicating that the drug release followed first order kinetics and also the drug release from microcapsules were by both diffusion and erosion

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