FORMULATION AND EVALUATION OF AMISULPRIDE LOADED INTRANASAL MICROEMULSION

Sachin N. Kothawade[a]* and Vishal V. Pande[a]

(Received 28 November 2022) (Accepted 22 August 2023)

ABSTRACT

The use of microemulsion as a delivery system for improving take-up across the nasal mucosa is currently being studied. A mucoadhesive polymer is added to help extend the retention time on the mucosa. The primary goal of the current research was to create a nano-formulation of amisulpride with the intention of increasing the drug's permeability and protecting it with a biocompatible lipid content, avoiding first-pass metabolism and efflux mechanisms, and selecting the route of administration to deliver amisulpride to the brain or CNS to increase the bioavailability of amisulpride at the targeted site of Schizophrenia. For calculating the percentage of transmittance, the release profile, and the levels of amisulpride in the brain and plasma, appropriate analytical methods were chosen, developed and validated. The results revealed that the residence time of ME (Microemulsion) was enhanced by the mucoadhesive agent and that a targeted site of action was achieved.

Keywords: Amisulpride, intranasal, microemulsion, mucoadhesive, schizophrenia, blood brain barrier

INTRODUCTION

Low bioavailability is caused by the high prevalence of poorly soluble drugs in the pharmaceutical industry. Due to the blood brain barrier (BBB) and the brain extracellular fluid barrier (BCSFB), drug delivery to the brain is extremely difficult[1]. Before electroconvulsive therapy (ECT) was available, various psychiatric interventions, including magic, restraints, emetics, purgatives, surgical procedures on various organs, removal of infection foci, vaccines and endocrinology, were attempted as treatment options for schizophrenia. It became possible to receive treatments like electroconvulsive therapy and insulin coma. However, Delay, Harl and Deniker's use of chlorpromazine to treat schizophrenia patients in the early 1950s marked the beginning of an era of drug therapy for the disease. Many medications have been examined and commercialised as antipsychotics over the following 50 years. In some ways, this drug class also aided in our understanding of the neurobiology of schizophrenia[2-4]. The clinicians' perspective on the expected result of the disorder has also changed because of this class of medication[3-5].

The use of microemulsion as a distribution system to improve take-up across the nasal mucosa is currently being studied. A mucoadhesive polymer is added to help extend the retention time on the mucosa. Due to their biocompatibility, biodegradability, simplicity in preparation and handling and, most importantly, their ability to solubilize both water- and oil-soluble drugs, microemulsions have garnered a lot of attention in recent years[5-6].

Intranasal microemulsion administration offers a useful, non-invasive alternate path of administration for the delivery of drugs to the brain, according to a literature review. Intranasal administration enables drug delivery to the brain by avoiding the BBB, offering a better method of brain targeting. Microemulsions reduce skin irritation, and they have been found to have a significantly lower potential for irritation when made without alcohol. The purpose of choosing a mucoadhesive microemulsion was to increase the drug's time in residence in the nasal mucosa so that it could be absorbed through the olfactory region and reach the brain without being limited by oral administration[7-10].

Microemulsions using temperature sensitive polymers are designed to have a longer nasal residence, and the microemulsion is adjusted in such a way that the formulation is in a liquid state on the shelf and gel upon administration. The properties of the gels can be modified suitably by optimising the formulation variable to obtain the desired biopharmaceutical performance[10-14].

[a] Department of Pharmaceutics, RSM's N.N Sattha College of Pharmacy, Ahmednagar - 414 001, Maharashtra, India
*For Correspondence: Email: Sachin.kothawade23@gmail.com

https://doi.org/10.53879/id.60.09.13783

The present research work involves the preparation of a mucoadhesive microemulsion of escitalopram oxalate to prolong nasal residence time. The formulation was evaluated for particle size, rheology, and *in vitro* safety evaluation studies.

MATERIALS AND METHODS

The drug sample of amisulpride was obtained from Elikem Pharmaceuticals Pvt. Ltd., Rakanpur, Gujarat. Surfactants Labrasol®, Tween® 20 and Tween® 80 obtained from ICI UK, Cremophor® RH-40 from BASF, India, Capmul® MCM from Abitech Corp. India. Co-surfactants methanol, PEG-600, propylene glycol, PEG-400 and Transcutol®-p from S. D. Fine Chem. Limited, Mumbai. All the other chemicals used were of AR grade, obtained from Research Lab. Fine Chem. Industries, Mumbai.

Solubility studies

By incorporating excess amisulpride into 2 mL of each oil in a centrifuge tube and blending on a rotary shaker (EOS-10M, Kytose Electrolab, Mumbai) at 25 ^{0}C and 250 rpm for 24 h, it was possible to determine the solubility of amisulpride in various oils. The specimens were centrifuged for 30 minutes at 5000 rpm before the supernatant was properly removed. After the appropriate dilution with methanol, the serial dilutions of supernatant were filtered through 0.45µm membrane filters, and the dissolution rate of amisulpride was assessed using a UV-visible spectrophotometer. The suitable oil, surfactant, and co-surfactant were dissolved to produce the blank in methanol as the sample.

Construction of pseudo-ternary phase diagram

For more research, emulsifier and founder were put into three different groups. This was done to find the right core proportion in the composition of microemulsion oil. The emulsifier and founder were combined in different volume ratios (S-mix) (1:1, 1:2, and 1:3). Such S-mix proportions have been selected to indicate an increase in founder concentration relative to emulsifiers and a decrease in founder concentration relative to emulsifiers to thoroughly analyse the phase diagrams in the formation of microemulsions. Aqueous phase titration was used to develop a pseudo-ternary phase diagram by adding water incrementally to an oil and S-mix mixture as phase diagrams were being constructed. Different oil as well as S-mix (V/V) ratios (1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, and 9:1) have been utilised for each phase diagram. After 5 minutes of stirring, a transparent and uniform oil/S-mix mixture was created. Each mixture was then titrated with water, and the results demonstrated clarity and flowability. Titration was stopped, when the system appeared turbid or bluish, and the pseudo-ternary phase graphs of the microemulsion region were then found and created using the "CHEMIX" ternary plot software.

Box-Behnken's optimisation study was conducted using Design-Expert software and a statistical design with three factors, three levels, and seventeen runs (Design Expert, version 7.0, Stat-Ease Inc., Minneapolis, USA). In this study, low, medium and high levels of the concentrations of oil (X1), surfactants (X2) and co-surfactants (X3) were chosen as distinct variables. According to the Box-Behnken design, the independent variables' main effects and interactions with one another's effects on the formulation's properties are explained. Maximising light transmission and drug loading while reducing the size of the particles and PDI was chosen as the study's objective function. The Box-Behnken design was chosen specifically because, in situations with three or four variables, it requires fewer runs than just a central composite design.

The Box-Behnken design was employed to systematically evaluate the individual and interaction effects of varying concentrations of oil (A), surfactant (B), and co-surfactant (C) on the particle size (R1), Polydispersity index (PDI) (R2), and% transmittance (R3) of microemulsion (Table I).

Table I: Variables in Box-Behnken design and their levels

Factor	Levels		
	-1	0	+1
Oil (mL) (X1)	4%	10	16%
Surfactant (mL) (X2)	20%	34	48%
Co-surfactant (mL) (X3)	36%	46	56%

Discovering three-dimensional response surfaces and building second-order polynomial models are both possible with this design. The multidimensional cube's centre point and the set of points located in the middle of each edge make up the design. These points define the region of interest.

The following describes the non-linear quadratic model produced by design: Yi is equal to b0, b1A, b2B, b3C, b12AB, b23BC, b13AC, b11A2, b22B2, and b33C3. Yi is the response corresponding to every input variable combination, while b0 is an intercept and b1 to b33 are the factor regression coefficients. The encoding levels of independent variables are A, B, and C. Table II lists

the dependent and independent variables that were chosen, as well as their high, medium, and low levels. The design called for the preparation of 17 batches of the ME formulation of amisulpride, which were then tested for responses like particle size (R1), PDI (R2), and percent transmittance (R3). To create a homogeneous, uniform, isotropic mixture, co-surfactant was also added while being continuously stirred for 20 minutes. The formulated L-ME was kept in storage at room temperature for future analysis.

Table II: Variables in Box-Behnken design and their constraint

R1	Particle size(nm)	Minimize
R2	Polydispersity index	Minimize
R3	% Transmittance	Maximize

R1- Particle size, R2- Polydispersity index (PDI), R3-Percent transmittance

Characterization of optimized batch

Clarity

Clarity was observed visually.

Centrifugation

The microemulsion structure was subjected to centrifugation for 15 minutes at 3000 rpm.

Measurement of % transmittance

Percent transmittance provided information on the formulation's clarity and transparency (percent T). Double distilled water was used to accurately dilute the microemulsion (10 mL). With water as a blank, this dilution was tested using a UV spectrophotometer at 650 nm.

PDI measurement and particle size

The improved amisulpride microemulsion and bioadhesive microemulsion formulations particle diameter and polydispersity index (PDI) were measured using a particle size analyzer (Nanophox Sympatech, Germany). The particle size was measured using double-distilled water, with the examination taking place at a temperature of 25 ^{0}C as well as a scattering angle of 90^0.

Viscosity measurement

Viscosity is a crucial characteristic to consider when determining the rheological behaviour of a microemulsion. With spindle No. 21, 25 ^{0}C., the Brookfield viscometer was used to determine the viscosity of the optimised microemulsion.

FTIR Spectroscopy

Amisulpride's IR spectrum was captured using a FTIR spectrophotometer (FTIR 4100, Jasco, Japan). Amisulpride and potassium bromide were combined (1:100), then the sample was triturated in a glass mortar before being placed in the specimen holder. The sample holder was placed in the analysis chamber. The spectrum was scanned over a frequency range of (4000 cm^{-1} – 400 cm^{-1}.)

In vitro drug release study

Tests were performed on drug solution, microemulsion (ME), and mucoadhesive microemulsion (MME) on the Franz diffusion cell (15 mL at 37^{0}C for 6 h with constant stirring at 400 rpm). Pre-soaking for 15 minutes in buffered phosphate (pH 6.4) with the dialysis membrane (lignocellulosic membrane, Mol. wt. 12000–14000 Da, pore size 2.4). A pre-soaked layer was attached between both the provider and recipient partitions of the diffusion cell, which had a cross-sectional area of 3.14 cm^2.

The amisulpride MME (1 mL) was distributed evenly over the membrane and firmly clasped in place from the donor chamber side. A sample (1 mL) from the receiver compartment was removed every hour, and it was replaced at 37 °C with a corresponding amount of fresh media. A microemulsion across a dialysis membrane was measured for percentage drug release using an ultraviolet spectrometer with a wavenumber of 225.2 nm.

RESULTS

Solubility studies

Amisulpride solubility in various oils

The ability of different oils, like Capmul® MCM, to dissolve amisulpride was tested to find out which oil was the best at doing so. The results showed that the solubility of amisulpride varied among the different oils tested. Fig. 1 represents the solubility of amisulpride in various oils. Capmul® MCM exhibited the highest solubility compared to the other oils. The drug concentration achieved in Capmul® MCM surpassed that of the other oils, indicating its superior solubilizing capacity for amisulpride.

Amisulpride solubility in various surfactants

The solubility of amisulpride in various surfactants, including Labrasol®, Tween® 20, Tween® 80 , Cremophor® RH-40 and others, was examined after choosing Capmul® MCM as the oil phase. The objective was to determine which surfactant had the greatest ability to saturate amisulpride. Fig. 2 represents the solubility of amisulpride

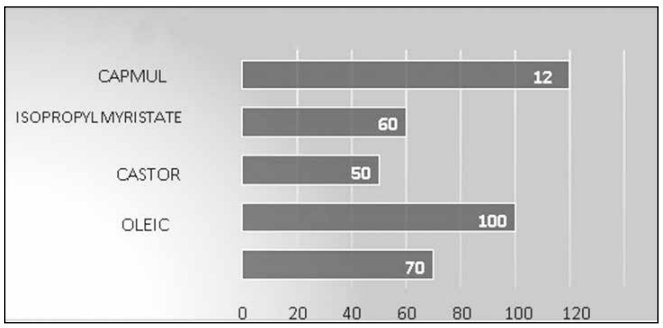

Fig. 1: Solubility of amisulpride in various oils

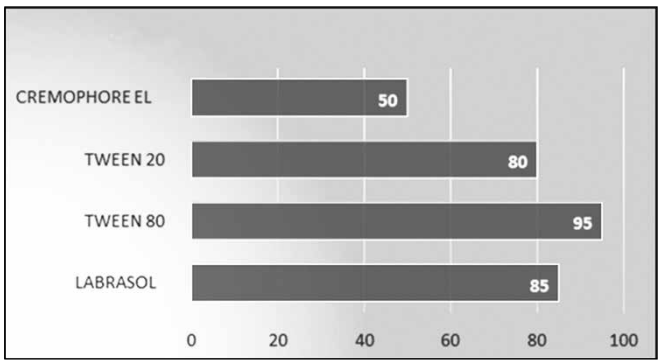

Fig. 2: Solubility of amisulpride in various surfactant

in different surfactants. Among the surfactants tested, Tween® 80 exhibited the highest solubility of the drug compared to the others.

Amisulpride solubility in various co-surfactants

The solubility of amisulpride was investigated in various co-surfactants, including methanol, PEG-600, propylene glycol, PEG-400, Transcutol®-p, and others, as shown in Fig. 3. Finding the co-surfactant with the greatest ability to solubilize amisulpride was the goal. According to solubility analysis, PEG-400 exhibited the

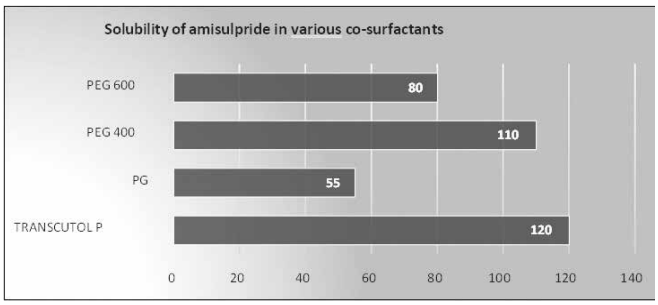

Fig. 3: Solubility of amisulpride in various co-surfactants

Table III: Composition of amisulpride microemulsion formulations

Run	Batch	Factor: A Oil	Factor: B Smix	Factor: C Water	Response R1 (PS)	Response R2 PDI	Response R3 % T
1	F1	10	20	56	95.84	0.77	97.12
2	F2	16	34	56	106.2	0.87	99.12
3	F3	10	48	36	103.2	0.79	97.34
4	F4	4	20	46	95.77	0.58	97.3
5	F5	10	34	36	95.79	0.56	98.2
6	F6	10	20	36	99.22	0.75	98.41
7	F7	10	34	46	98.07	0.77	98.79
8	F8	4	48	56	99.12	0.95	97.3
9	F9	4	34	36	107.3	0.79	99.12
10	F10	10	34	46	96.22	0.46	97.04
11	F11	16	34	46	101.88	0.78	98.88
12	F12	4	48	46	96.33	0.77	97.04
13	F13	10	48	46	105.2	0.91	98.88
14	F14	16	34	46	95.79	0.66	96.99
15	F15	10	20	46	111.11	0.92	99.11
16	F16	16	34	46	98.22	0.76	98.33
17	F17	10	34	46	98.15	0.74	98.02

The data are presented as mean SD (n=3).

R1 (PS)- Particle Size, R2 (PDI)- Polydispersity index, R3 (%T)- Percent transmittance

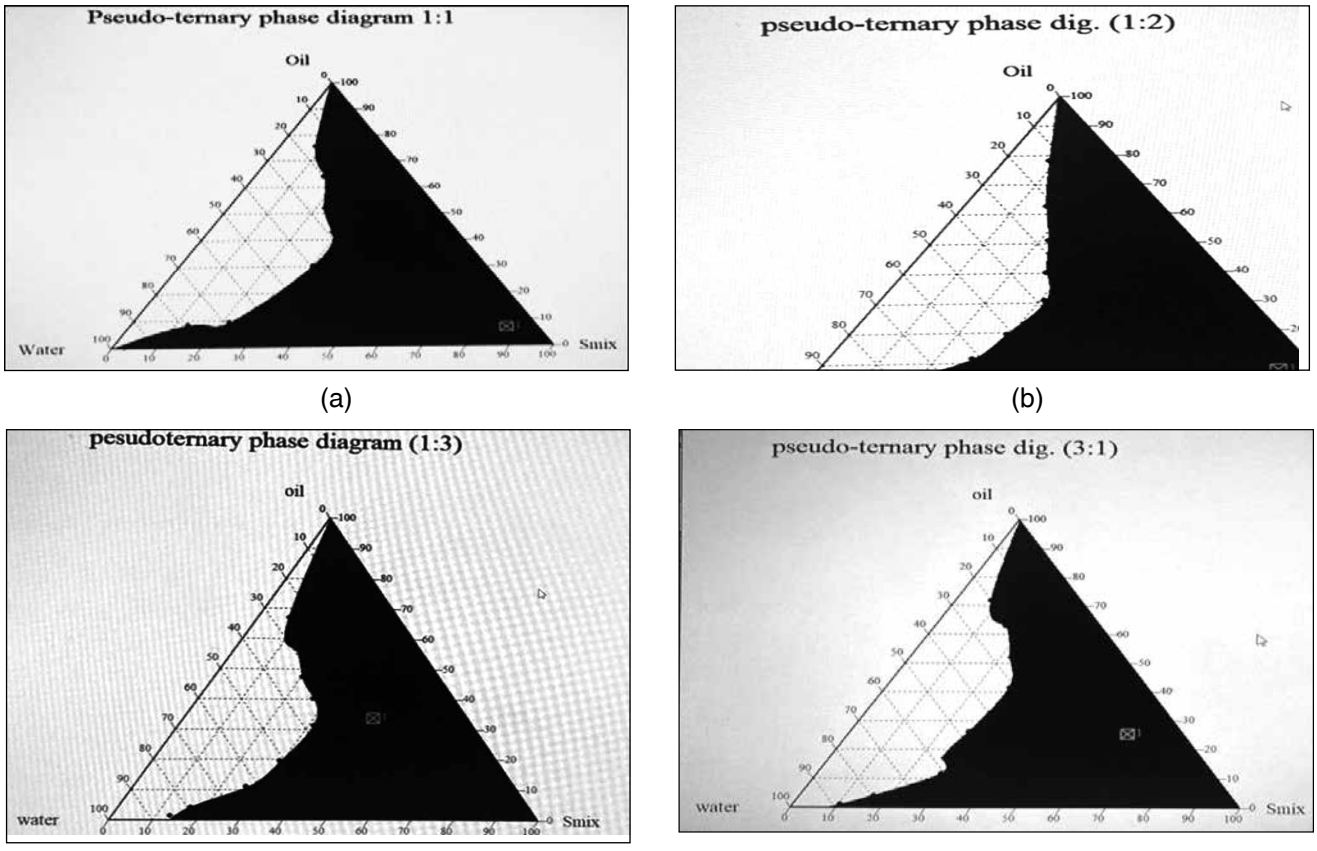

Fig. 4: Pseudo ternary phase diagrams at various ratios a) 1:1 b) 1:2 c) 1:3 d) 3:1

highest solubility of amisulpride compared to the other co-surfact ants tested.

Pseudo ternary phase diagram construction

By adjusting the ratio between the oil concentration and the surfactant mixture, or Smix, pseudo-ternary phase representations have been generated. The titration process involved increasing the amount of oil (90 %) while decreasing the concentration of Smix (10 %) in the aqueous phase. Additionally, titration was performed using the lowest oil concentration and the highest Smix ratio concentration. The pseudo-ternary diagrams were studied using Capmul® MCM oil and altering the ratios of five S-mix factors (Tween® 80: Transcutol®-P) as follows: 1:1, 1:2, 1:3, and 3:1. Fig. 4 illustrates the results of the pseudo-ternary diagrams. The phase diagram analysis indicated that the S-mix ratios of 1:1, 1:2, and 1:3 suggested a smaller area of tiny emulsification compared to the 3:1 ratio. Therefore, further investigation was carried out using the 3:1 S-mix ratio. In Fig. 4, the pseudo-ternary diagrams were evaluated using the Smix ratios of 1:1, 2:1, and 3:1. The results showed that the Smix ratios of 1:1, 2:1, and 3:1 indicated a smaller area of micro emulsification compared to the 3:1 ratio, as observed in the phase diagram analysis. Consequently, the 3:1 S-mix ratio was selected for additional investigation.

Amisulpride ME formulation optimization

Amisulpride's liquid microemulsion (ME) formulation was optimized, and based on the formulation variables, the responses (R1-particle size in nm, R2-polydispersity index, and R3-percent transmittance) were calculated. The Design Expert 13.0 software was used to investigate the effects of independent variables on the results. Table III presents the design of the experiment architecture for 17 potential batches of amisulpride's liquid ME formulation. Various models, including linear, 2FI (2-factor interaction), quadratic, and cubic models, were suggested and evaluated using the software's analysis of variance (ANOVA), which worked well for the analysis. Individual dependent variable regression polynomials were created, and contour plots and 3D surface graphs were generated for each dependent variable to visualize the effects of the variables.

The statistical results of the models are presented in Table IV. Mathematical models were developed and expressed in the form of equations for each dependent

Table IV: ANOVA for response surface quadratic model

	R1		R2		R3	
	F value	P value	F value	P value	F value	P value
Model term	5.44	0.0180	6.53	0.0109	4.04	0.0396
A	40.00	0.0004	49.64	0.0002	23.12	0.0019
B	0.0699	0.7991	1.75	0.2280	0.8286	0.3930
C	1.27	0.2976	0.7756	0.4077	4.26	0.0778
AB	1.60	0.2459	2.42	0.1635	0.0008	0.9785
AC	0.0897	0.7733	0.0242	0.8807	2.82	0.1370
BC	0.0188	0.8949	0.0242	0.8807	1.36	0.2818
A^2	5.26	0.0555	0.0367	0.8534	1.38	0.2783
B^2	0.4380	0.5293	3.55	0.1014	1.90	0.2100
C^2	0.0063	0.9388	0.6899	0.4336	0.7956	0.4020

(*Model terms are considered significant when the P-value is less than 0.0500)*

R1- Particle size, R2- Polydispersity index (PDI), R3-Percent transmittance

variable (R1, R2, and R3). The effects of the variables on the responses are represented by the coefficients of R1, R2, and R3, where a coefficient with a positive value denotes an expanding effect and a coefficient that is negative indicates a contracting effect.

The model F-values for responses R1, R2, and R3 were observed to be 5.44, 6.53, and 4.04, respectively. These results show that the selected exponential model became significant for each of the three responses. Additionally, examining the "prob > F" value—a value of 0.05 indicating significance-helped to determine the significance of the model terms. The software generated surface response analysis plots in three-dimensional design graphs to visualize the interactions between the effects of the independent factors on the responses. These plots, with the third factor held constant, were used to analyze the interactions between the two independent factors.

Effect of formulation variable on particle size

The effect of formulation variables on the particle size (R1), polydispersity index (R2), and percent transmittance (R3) of the amisulpride microemulsion (ME) formulation was studied. The surface plots and mathematical models were generated to analyse the relationship between the independent variables and the responses.

Particle size (R1)

The surface plot for particle size showed that a decrease in the Smix proportion and an increase in the oil phase ratio (Capmul® MCM) resulted in an increase in particle size. The quadratic model was found to be significant, with a model F value of 5.44 and P values less than 0.05 for each term. The significant model terms were X1 (Smix proportion), X2 (oil phase concentration), and X3 (water concentration). The equation for the particle size response (R1) indicates that an increase in the concentration of Smix and oil has a favourable impact on particle size, while water concentration has a detrimental effect.

Polydispersity index (PDI) (R2)

The PDI represents the homogeneity and consistency of the formulation, with lower values indicating better uniformity. The PDI surface plot demonstrated that a rise in PDI was caused by a decrease in the Smix proportion as well as a rise in the oil phase level (Capmul®). The quadratic model was found to be significant, with a model F value of 6.53 and P values less than 0.05 for each term. The significant model terms were X1, X2, and X3. The equation for the PDI response (R2) shows that the concentration of Smix and oil has a positive effect on PDI, while the concentration of water has a negative effect.

Percent transmittance (% T) (R3)

The percent transmittance measures the transparency of the formulation, with higher values indicating better transparency. The surface plot for %T demonstrated that a decrease in the Smix proportion and an increase in the oil phase concentration (Capmul® MCM) led to a decrease in %t. The quadratic model was found to be significant, with a model F value of 4.04 and a P value of 0.0050. The significant model terms were X1, X2, and X3. The equation for the % T response (R3) shows that the concentration of Smix and oil has a negative effect on % T.

Characterization of optimized batch

Particle size

The optimised batch (F6) of the amisulpride microemulsion formulation had a particle size of 104.58±2.4 nm. This indicates that the formulation achieved the desired particle size range, which is important for stability and efficient drug delivery. The narrow polydispersity index of 0.9 suggests a relatively uniform particle size distribution, indicating good homogeneity of the formulation.

% Transmittance

The optimised batch (F6) demonstrated a high percent transmittance of 97.76 %. This indicates that the formulation is transparent, which is desirable for an

Table V: Reported and observed frequency of amisulpride

Functional group	Reported peak frequencies (cm^{-1})	Observed peak frequencies (cm^{-1})
N—H (Amine)	3300-3350	3312.14
N—H(Amide)	3100-3500	3410.9
C—O (Ether)	1070-1150	1127.19
C—C (3° Amine)	1400-1600	1489.74
O=S=O	1360-1400	1362.4

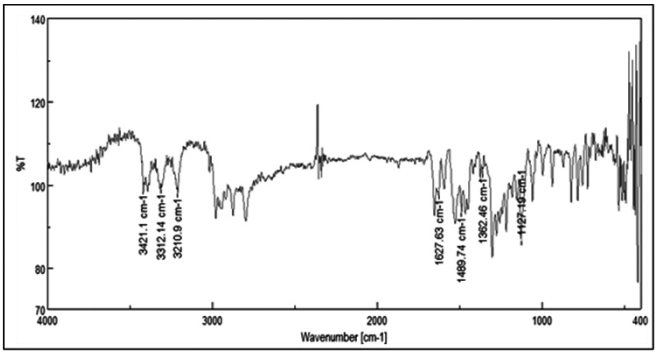

Fig. 5: FTIR of amisulpride

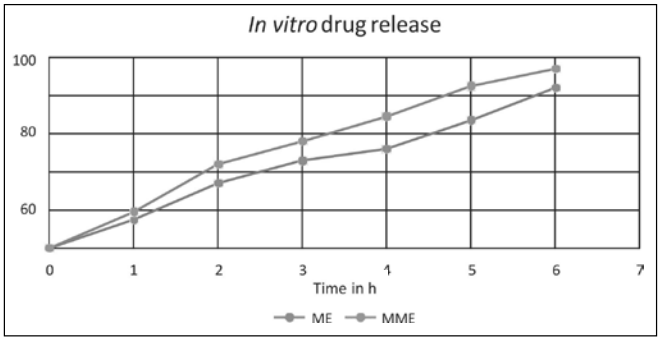

Fig. 6: Comparative % drug release of ME (Microemulsion) and MME (Bioadhesive microemulsion)

isotropic and visually appealing formulation. The high transmittance value suggests that the formulation has good clarity and may enhance drug bioavailability due to better dispersion in the biological environment.

FTIR spectroscopy

FTIR spectroscopy was used to figure out what kind of functional groups were present in the microemulsion formulation of amisulpride. The IR spectra, as shown in Fig. 5, provided information about the chemical bonds and molecular structure of the formulation. Table V presents the characteristic functional groups observed in the FTIR spectrum. This analysis helps to confirm the presence of amisulpride and other excipients in the formulation and provides insights into their interactions.

In vitro drug release study

To assess the release profile of amisulpride from the optimised microemulsion formulation (ME) and the *in-situ* gelling bioadhesive microemulsion (MME), an *in vitro* drug release investigation was carried out. The results showed that the ME formulation achieved a drug release of 84.27 %, while the MME formulation exhibited a higher drug release of 94.08 %, as shown in Fig. 6. This suggests that the microemulsion formulation enhances drug solubility and facilitates drug release. The incorporation of the drug in the microemulsion system improves its aqueous solubility, leading to enhanced drug release. The initial burst release observed in the MME formulation can be attributed to the presence of chitosan, a mucoadhesive agent that promotes higher drug release and facilitates solubilization at low concentrations. However, the release of drug at later stages was hindered due to the extensive cross-linking of chitosan at different pH levels, resulting in pH-dependent gelling. This controlled release behaviour may be advantageous in situations requiring immediate therapeutic intervention, such as in psychotic episodes, where a higher initial burst release is preferred for rapid drug action.

DISCUSSION

The solubility of a drug in different oils, surfactants, and co-surfactants is crucial for formulating effective drug delivery systems. In this study, the solubility of amisulpride was looked at in different oils, surfactants, and co-surfactants to find the ones that could dissolve it the best.

The results showed that Capmul® MCM exhibited the highest solubility for amisulpride among the tested oils. This suggests that Capmul® MCM possesses excellent solubilizing properties and can effectively dissolve amisulpride at a high drug concentration. Similarly, Tween® 80 was found to have the highest solubility among the surfactants tested, indicating its superior solubilizing capabilities for amisulpride. PEG-400 was identified as the co-surfactant with the highest solubility for amisulpride.

Based on these results, Capmul® MCM, Tween® 80, and PEG-400 were chosen as the best excipients for making amisulpride easier to dissolve in the next round of formulation development. These choices ensure that the drug can be incorporated into stable emulsion or micellar systems, enhancing its solubility and potential therapeutic efficacy.

The analysis of these diagrams showed that certain ratios of Smix (a mixture of surfactants and co-surfactants) and oil concentrations had smaller areas of emulsification, which meant that the emulsion systems were more stable and desirable.

The optimisation of the amisulpride liquid microemulsion formulation was conducted using Design Expert software. The quadratic model was found to be significant for all three responses: particle size, polydispersity index (PDI), and percent transmittance (% T). The mathematical models developed for each response provided equations expressing the relationship between the independent variables and the responses. The coefficients in these equations indicate the magnitude and direction of the effects of the variables on the responses.

"The surface response analysis plots helped in understanding how changes in variables affected the responses and in identifying optimal regions within the design space by visualising the interactions between the independent factors and the responses." The ANOVA study confirmed the significance of the model terms and the overall performance of the quadratic model.

The optimised batch of the amisulpride microemulsion formulation demonstrated desirable particle size, good transparency, and controlled drug release behaviour. The particle size fell within the desired range, indicating stable and uniform droplet formation. The high percent transmittance suggested good clarity and dispersion of the formulation. The FTIR spectroscopy analysis confirmed the presence of characteristic functional groups. The *in vitro* drug release study showed significant drug release, with the *in situ* gelling bioadhesive microemulsion exhibiting a higher initial burst release followed by sustained release.

This study identified Capmul® MCM, Tween® 80, and PEG-400 as the preferred excipients for solubilizing amisulpride. The pseudo-ternary phase diagrams aided in selecting the optimal Smix ratios. The optimisation process using Design Expert software provided insights into the effects of independent variables on particle size, PDI, and % T. The characterization of the optimised batch confirmed the desirable properties of the amisulpride microemulsion formulation. These results will help to make a stable and effective drug delivery system for amisulpride with better solubility and possible therapeutic benefits.

CONCLUSION

The basic goal of the current research was to develop and design a microemulsion of amisulpride with the intention of increasing drug permeability and protection with biocompatible lipid content, avoiding first pass metabolism and efflux mechanisms, and choosing the path of administering amisulpride to the brain or CNS to increase amisulpride's bioavailability at the targeted site of schizophrenia. For calculating the percentage of transmittance, the *in vitro* drug release profile, and the levels of amisulpride in the brain and plasma, appropriate analytical methods were chosen, developed, and validated. The outcome showed that the mucoadhesive agent increased the retention time of ME and that the specific target site of action was achieved. As a result, this microemulsion technology is a promising method for amisulpride to target the brain in the diagnosis of antipsychotics.

REFERENCES

1. Alagusundaram M. and Chengaiah. B.: Nasal drug delivery system an overview, **IJRPS Pharmascope**, 2010, 5(77), 454-465.
2. Chan J., Gamal M., Maghraby E. and Jenniffer P.: Phase transition water-in-oil microemulsions as ocular drug delivery systems: *in vitro* and *in vivo* evaluation, **Int. J. Pharm.**, 2013, 328(1), 65-71.
3. Chime S. and Onyshi V.: Lipid based drug delivery systems (LDDS): Recent advanced and application in drug delivery, **Afr. J. Pharm. Pharmacol.**, 2013, 7 (8), 3034-3059.
4. Guo J., Kim K. H. and Nandi I.: Development of ethyl laurate based microemulsion for rapid onset of intranasal drug delivery of diazepam, **Int. J. Pharm.**, 2017, 237 (1-2), 77-85.
5. Haque K. M. and Hasan A. H.: Intranasal *in situ* gel loaded with saquinavir mesylated nanosized microemulsion: preparation characterization and *in vivo* evaluation, **Int. J. Pharm.**, 2012, 4(475), 191-197.
6. Hyun-Jong D., Abrahamson M., Kapoor Y. and Chauhan A.: Timolol transport from microemulsion trapped in HPMC gels, **J. Colloid Interface Sci.**, 2011, 7 (315), 297- 306.
7. Kiruba F., Lahan M., Babbar A. and Kaul A.: Intranasal clobazam delivery in the treatment of status epileptics, **J. Pharm. Sci.**, 2008, 100(2), 629-703.
8. Kiruba M., Hyun-Jong, Ubonvan T. and Hyung-Tae.: Development of udenafil-loaded microemulsion for intranasal delivery: *In vitro* and *in vivo* evaluation, **Int. J. Pharm.**, 2010, 7(12) 27-38.
9. Linaley G. and Sraff C. L.: Nasal drug administration: Potential for targeted central nervous system delivery, **J. Pharm. Sci.**, 2002, 8 (94), 1187-1195.
10. Rajput A. and Patil V.: Nose to brain delivery of ziprasidone microemulsion: Design and characterization, **Int. Res. J. Pharm.**, 2013, 4 (7), 170- 177.
11. Mandal A., Stolnik S. and Illum L.: Nanoparticle for direct nose-to-brain delivery of drugs, **Int. J. Pharm.**, 2016, 8 (379), 146-157.
12. Misra M., Pathak R., Dash R. P. and Nivsarkar M.: Role of mucoadhesive polymers in enhancing delivery of nimodipine microemulsion to brain via intranasal route, **Acta Pharm. Sin. B**, 2014, 4(2), 151-160.
13. Patel R. B., Bhatt K. K. and Patel B. G.: Formulation and evaluation of microemulsion based drug delivery for intranasal administration of olanzapine, **Int. J. Biomed. Pharm. Sci.**, 2013, 4(7), 7-20.
14. Rao Y. S., Deepthi K. S. and Chowdary K. P.: Microemulsion: A novel drug carrier system, **Int. J. Drug Del. Technol.**, 2009, 1(2), 39-41.