INTERNATIONAL RESEARCH JOURNAL OF PHARMACY
www.irjponline.com
ISSN 2230 – 8407

Research Article

COMBINATION OF METFORMIN AND CURCUMIN THERMOREVERSIBLE NASAL *IN SITU* GEL FORMULATION AND *IN VITRO-EX VIVO* EVALUATION FOR DIABETES-INDUCED ALZHEIMER'S DISEASE

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Article Received on: 05/06/21 Approved for publication: 02/07/21

DOI: 10.7897/2230-8407.1206140

ABSTRACT

The present research was focused to prepare the formulation containing combination of Metformin and Curcumin to control diabetes-induced Alzheimer's in elderly population with the utilization of Poloxamer P188 (8%), a thermoreversible gelling polymer, and mucoadhesive polymers such as Carbopol 940, Sodium alginate and HPMC K100 in varying concentrations (0.5%, 1%, 1.5% and 2% respectively) to improve the absorption of drugs by increasing the contact time with nasal mucosa. The *in situ* gel was prepared by cold method and administered via nasal route to deliver the drug directly to CNS by bypassing BBB and to improve patient compliance, nasal bioavailability of drugs by cumulative its nasal retention time in nasal mucosa. Total 12 nasal *in situ* gels were prepared and evaluated for *in vitro* studies and *ex vivo* drug diffusion studies (goat nasal mucosa) and results were found to be satisfactory. Moreover, histopathological studies revealed that the preparation was safe to be used on nasal mucosa of goat. The prepared nasal *in situ* gel is an effective alternative to conventional method and can be used to treat diabetes-induced Alzheimer's disease.

Keywords: Metformin, Curcumin, Thermoreversible polymer, Mucoadhesive polymer, *In situ* gel, Cold method

INTRODUCTION

The most preferable route is oral route for administration of drug. In spite of being convenient route due to several reasons such as degradation of drug and several associated side effects caused in stomach makes it non desirable and inferior to other route of administration of therapeutic agents. Scheme for delivering drugs through nose identified as an appropriate favourable route for delivery of therapeutic agents due to improved systemic bioavailability of drugs and its delivery directly to brain by circumventing the BBB [1-2].

Pathway involved in delivery of drug from nose to brain [1-2]

The route engrossed in the delivery of therapeutic agents from nose via mucosal membrane to the brain is the combination of CSF, Lymphatic and Vasculature system. (Figure 1)

Thermoreversible *In situ* Gels [3-4]

Thermoreversible *In situ* gels are the drug delivery system which uses temperature sensitive polymers that are initially in solution form at room temperature(19°C-25°C) and undergoes gelation when come in connection with the body at body temperature.

Advantages

- Improved retention time.
- Dosing frequency of drug is reduced.
- Low dose required.
- Bioavailability of drug is improved
- Direct delivery of drug to CNS by bypassing BBB.
- Improved patient compliance.

Diabetes-induced AD

Diabetes-induced AD called as 'Type 3 diabetes'. Many epidemiological evidences show that compared with nondiabetic patient, diabetics has high risk of getting AD. The risk of getting AD is allied with oxidative stress, insulin resistance, inflammation, hyperglycaemia, advanced glycation end products (AGEs) and autophagic dysfunction which are caused diabetic patients [5-6]. (Figure 2)

Combination of Metformin with Curcumin for diabetes-induced AD

Metformin is the most extensively used biguanide class of antidiabetics to treat diabetes. It increases the liver and muscle cell's sensitivity to insulin through AMP-mediated route. It is a neuroprotective which decreases the phosphorylation of the insulin receptors and enhanced neuronal survival, apart from its anti-hyperglycaemic activity [17,18].

Curcumin inhibits the aggregation of amyloid-β (Aβ) protein and inflammation induced by Aβ as well as β-secretase and acetyl-cholinesterase activities. It enhances the behavioural impairment in AD patient's brain by inhibiting Aß and tau phosphorylation [19]. Combination of Curcumin with Metformin act synergistically on oxidative stress and dyslipidaemia, and enhanced PON 1 level which are major cause of AD. Therefore, it is a promising strategy for combating diabetes-induced Alzheimer's complications [21].

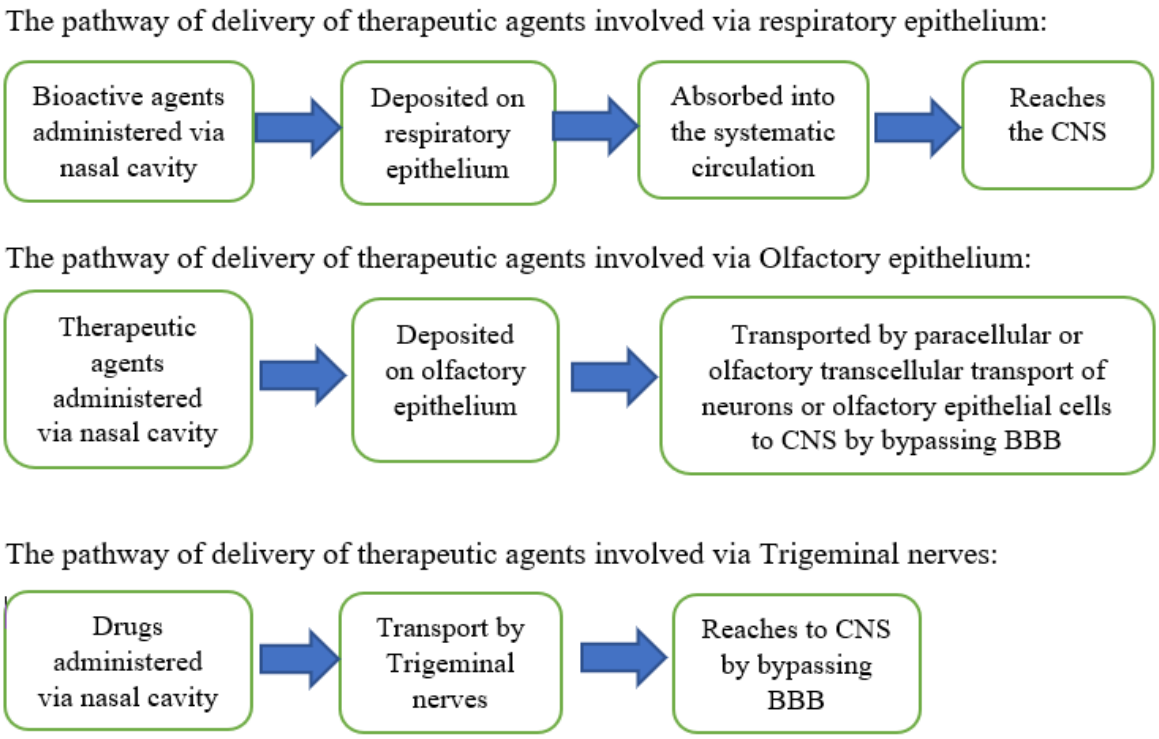

Figure 1: Pathway of delivery of drug to brain

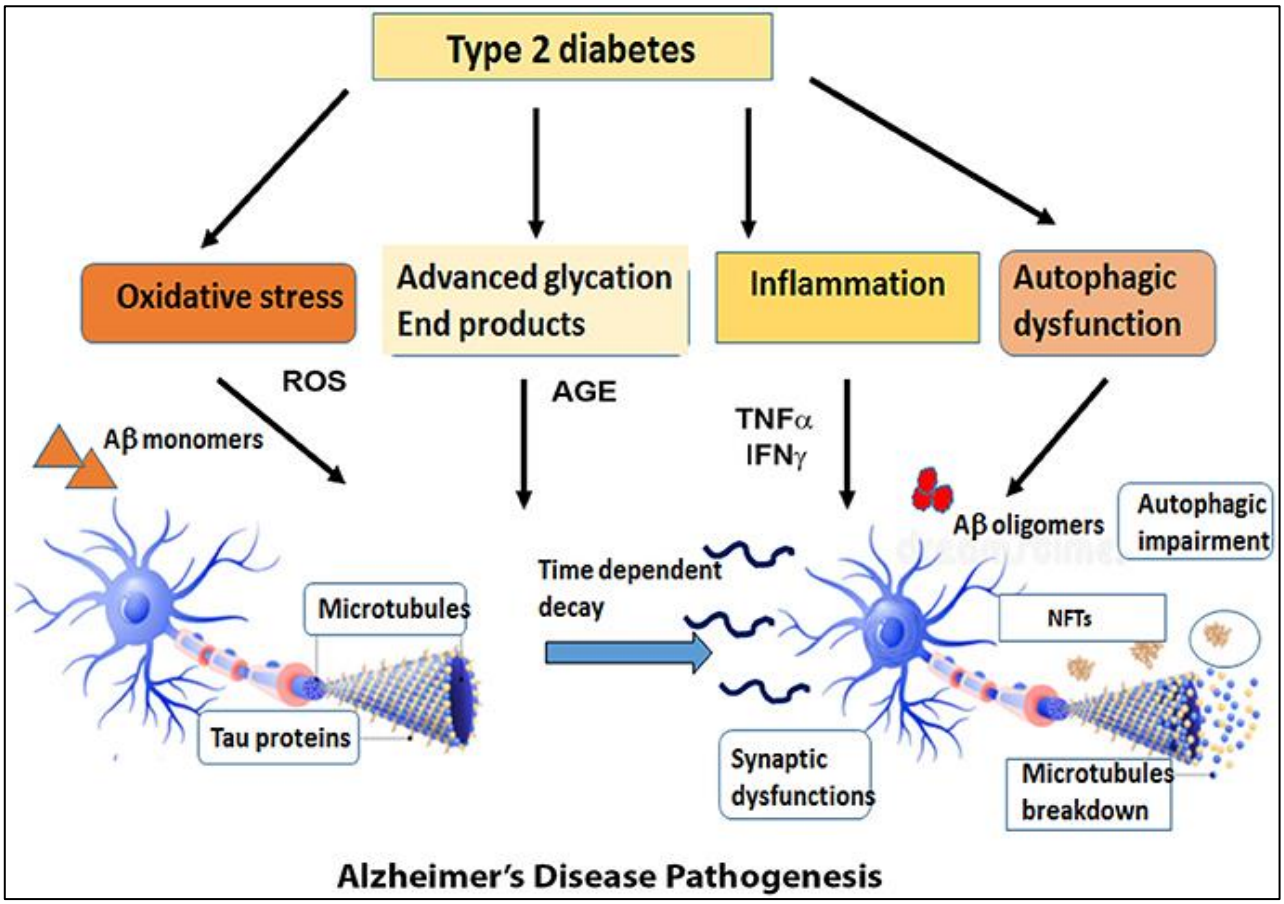

Figure 2: Alzheimer's disease pathological process

MATERIALS AND METHODS

Metformin as gift sample received from Aurobindo Pharma Pvt. Ltd., Hyderabad(India). Curcumin(95% purity) procured from Yarrow chem Pvt. Ltd., Mumbai(India) and other chemicals namely, HPMC K 100, Carbopol 940, Sodium alginate and Benzalkonium chloride were received from Research Laboratories Pvt. Ltd., Hyderabad(India) and Hydroxy-β-cyclodextrin and Poloxamer 188 received as gift sample from Mylan Laboratories Pvt. Ltd., Hyderabad(India).

Characterization of Drugs

FTIR- Fourier Transform Infrared Spectroscopic Studies
FTIR is used to study the drug-excipient compatibility. It is also used to identify the inorganic or organic materials present in the compound. The peaks were obtained at 3372, 3451 and 2884 cm^{-1}.

UV Spectroscopy
The maximum absorbance for Metformin was obtained at 233 nm and for Curcumin at 423 nm in pH 6.4 phosphate buffer solution.

Thermoreversible-Mucoadhesive Nasal *in situ* Gel preparation

Preparation of gels was done by cold method. Hydroxypropyl-β-cyclodextrin was initially agitated in appropriate volume of distilled water at room temperature then drugs Metformin and Curcumin was stirred with sufficient quantity of distilled water and kept at temperature maintained for 4˚C in a refrigerator then methylparaben were successively added in the above drugs solution. After cooling to room temperature, Poloxamer P188 and other *in situ* gelling polymers were gradually added to above solution and stir until they dispersed completely. To get clear solution this dispersion was stored at 4ºC overnight. Finally, the volume was adjusted to the indispensable volume with distilled water.

EVALUATION OF QUALITY CONTROL PARAMETERS OF DRUG NASAL *IN SITU* GELS [14-15]

Clarity
Clarity test was done by visual inspection.

Viscosity
Brookfield viscometer was used to measure viscosity with spindle number 64 at 100 rpm at altered temperature ranges between 4 ºC - 37ºC. The spindle number 64 kept constant for each batch and put the solution in water bath to increase the temperature. The viscosity graph against temperature was plotted. The measurement was carried out in triplicate.

Measurement of pH
It was measured by using digital pH meter by taking 1 ml of each preparation and add up to 25 ml with distilled water in beaker. The pH determination was carried out in triplicate.

Drug Content
1 ml of preparation in 10ml volumetric flask, diluted with 6.4 pH phosphate buffer and final volume made up to 10 ml. 1 ml of this solution was again diluted to get 5 ml with 6.4 phosphate buffer. Absorbance of final solution was precised by UV-Vis Spectrophotometer at λmax 233nm and 423nm.

$$Drug\ content = Conc. \times Df \times \frac{volume\ of\ stock}{Conversion\ factor}$$

Gelation Temperature
The preparation was cooled to 4 ºC initially then, 20 ml of the solution in 25 ml beaker was placed on a hot plate magnetic stirrer with magnetic bead in it with constant stirring at 100 rpm and temperature is increased with 1 ºC per min. When magnetic bead rotation gets stopped at particular temperature noted as the gelling temperature of that particular formulation. The evaluation of temperature was carried out in triplicate and average value was taken.

Mucoadhesive Force
The adhesive tendency of each formulated solution was resolute by assessing the strength needed to separate the preparation of nasal mucosal tissues using a modified analytical balance in laboratory. Part of the goat's nasal mucosa was stored in Tyrode solution. The mucosal layer was fixed on each glass vial using thread and would be stored for 5 min at 37ºC. The adhesive strength, expressed as dyne/cm² as separation tension, was calculated using following equation,

$$Detachment\ tension = m \times g \div a$$

Ex vivo diffusion studies
The test was done by Franz diffusion cell inserted with goat nasal mucosal tissue as diffusion membrane. Before starting the experiment, the mucosal membrane was soaked in 6.4 pH phosphate buffer for 24 hrs. The mucosal membrane was inserted in between donor and receptor compartment and filled with 6.4 phosphate buffer solution with temperature maintained at 37°C with constant stirring by magnetic stirrer. 2 ml of preparation was taken in the donor compartment. At every hour, 2 ml of sample was taken out from the receptor compartment and after each sampling the sampled volume is replaced with fresh phosphate buffer pH 6.4 for 6 hrs. The absorbance was spectrophotometrically determined at λmax 233 nm and 423 nm using pH 6.4 phosphate buffer as blank. The studies are carried out in triplicate.

$$\%\ CDR = \frac{Amount\ of\ drug\ release}{Amount\ of\ drug\ loaded} \times 100$$

Histopathological Studies
The histopathological studies were carried out for optimized formulation. The two mucosal membranes were cut into pieces (2 cm²) and were fitted on *in vitro* diffusion cells. One mucosa treated with 1 ml of 6.4 pH phosphate buffer (control) and the other treated with 1 ml of optimized formula (test) and kept in incubator. The sections of both control and test mucosa checked under microscope to check any major changes in the morphological structure of mucosa and also changes in epithelial cells when treated with formulation.

Stability Study
To check shelf life the tests were done for an optimized formula in screw capped vial in accordance with the ICH guidelines and stored in desiccators provided 75 ± 5% relative humidity and 40 ± 2 °C temperature maintained for three months and evaluated for different parameters such as %drug release and other factors.

RESULTS

Preformulation studies

Melting point determination
The melting point of Metformin was obtained at 224.5ºC and Curcumin 183ºC.

Solubility

Solubility test done with different solvents such as water, ethanol, acetone and chloroform.

Table 1: Solubility of Metformin and Curcumin in various solvents

Solvents	Metformin	Curcumin
Ethanol	Slightly soluble	freely soluble
Water	Freely soluble	Slightly soluble
Acetone	Insoluble	Soluble
Chloroform	Insoluble	Soluble

Estimation of Drugs by UV spectroscopy

Determination of λmax

The λmax of Metformin drug was found to be at 233nm and for Curcumin it was at 423nm.

Calibration curve

Calibration of Metformin and Curcumin in pH 6.4 phosphate buffer was plotted graphically and shown in figure 3 and 4 respectively.

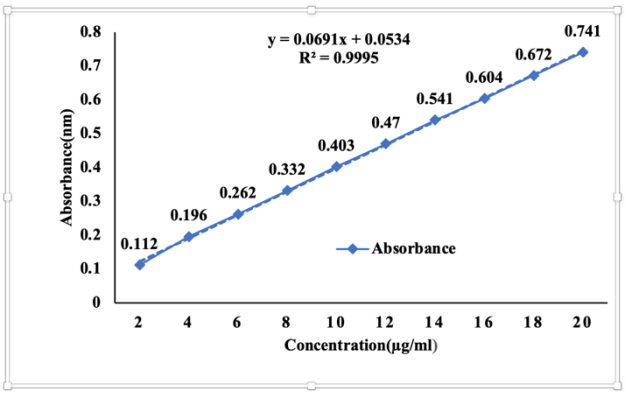

Figure 3: Standard graph of Metformin at 233nm

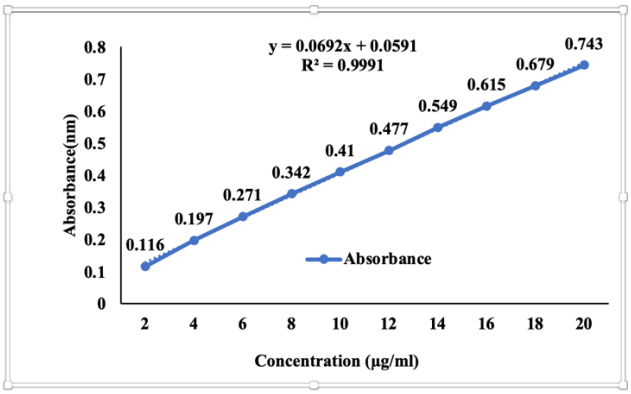

Figure 4: Standard graph of Curcumin at 423nm

Compatibility studies

FTIR Spectroscopy

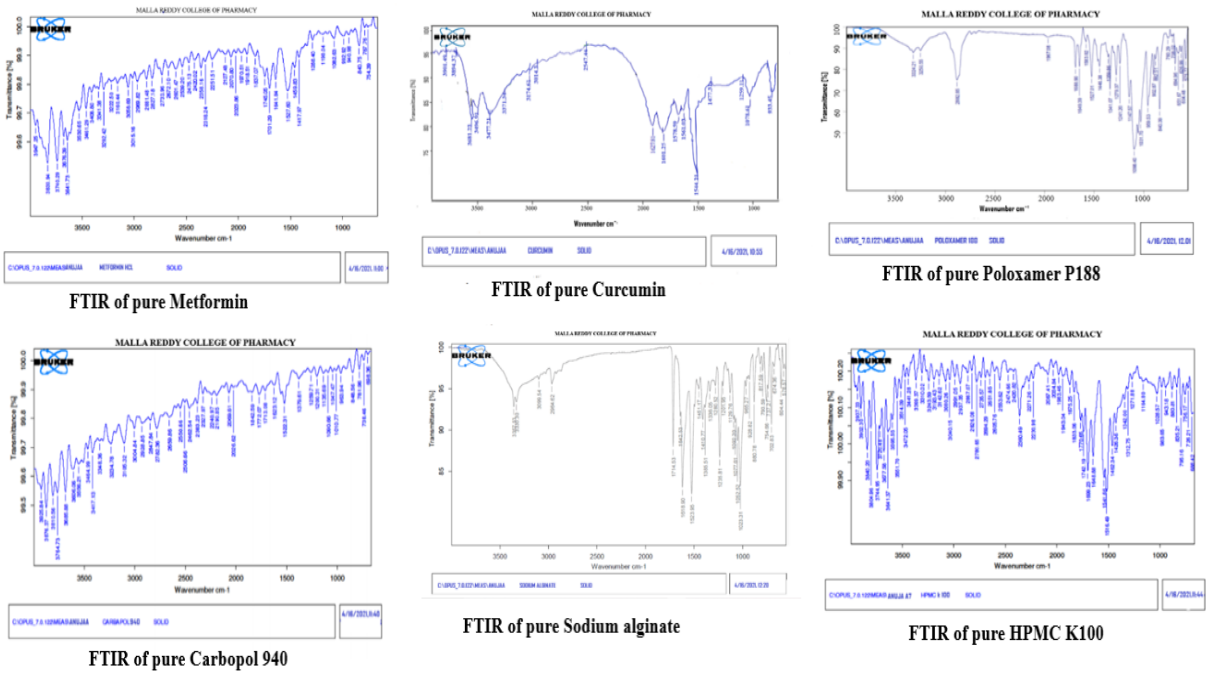

Figure 5: FTIR of pure drugs and polymers used

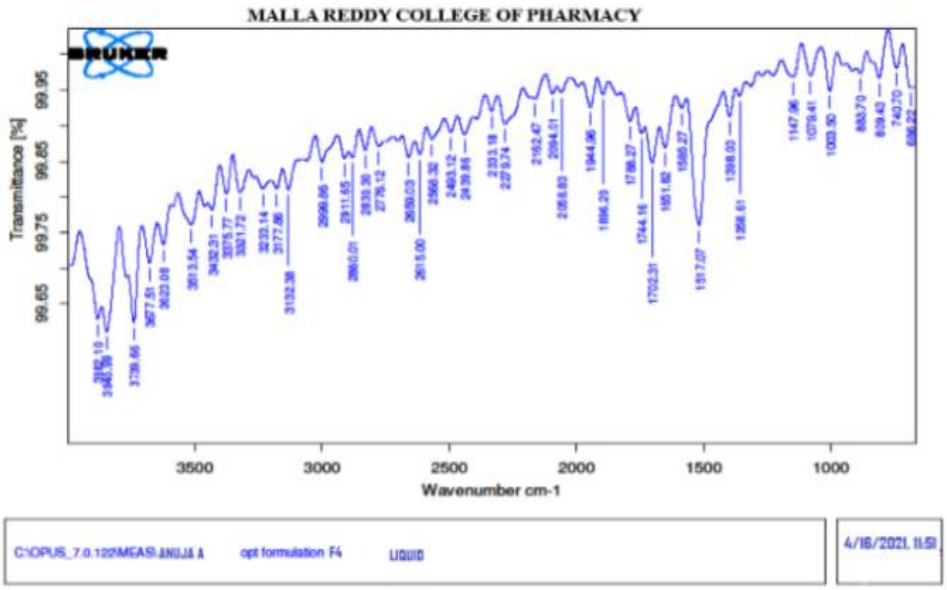

Figure 6: FTIR of Optimized formula (FC4)

Formulation development

Formulation design

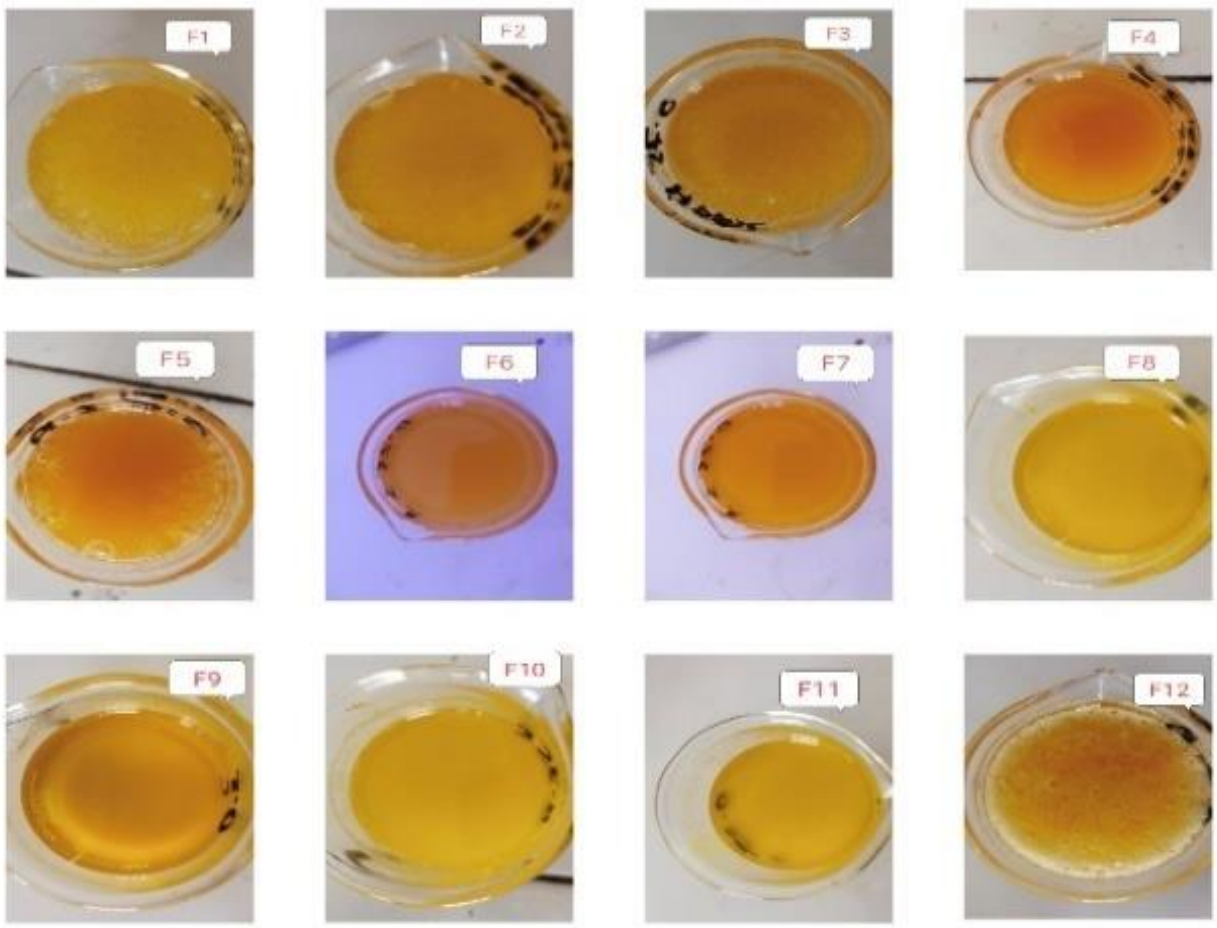

Figure 7: Formulations with different polymers

Table 2: Formulation of *in situ* gels by cold method

Formulation code	FC1	FC2	FC3	FC4	FS5	FS6	FS7	FS8	FH9	FH10	FH11	FH12
Metformin(mg)	500	500	500	500	500	500	500	500	500	500	500	500
Curcumin(mg)	200	200	200	200	200	200	200	200	200	200	200	200
Poloxamer P188(g)	8.1	8.1	8.1	8.1	8.1	8.1	8.1	8.1	8.1	8.1	8.1	8.1
Carbopol 940(g)	0.25	0.5	0.75	1.0	-	-	-	-	-	-	-	-
Sodium alginate(g)	-	-	-	-	0.25	0.5	0.75	1.0	-	-	-	-
HPMC K 100(g)	-	-	-	-	-	-	-	-	0.25	0.5	0.75	1.0
Methyl paraben(g)	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Benzalkonium chloride(ml)	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02
Glycerin(ml)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Hydroxypropyl-beta-cyclodextrin(g)	2.1	2.1	2.1	2.1	2.1	2.1	2.1	2.1	2.1	2.1	2.1	2.1
Distilled water Q.S. (ml)	50	50	50	50	50	50	50	50	50	50	50	50

Evaluation of Thermoreversible nasal *in situ* gels

Table 3: Effect of temperature on viscosity

Formulation code	Viscosity in cp± SD(n=3)	
	At 4ºC(100rpm	37ºC(100rpm)
FC1	456±0.00	3819±0.00
FC2	486±0.34	3910±0.34
FC3	516±0.67	4256±0.50
FC4	578±0.34	4530±0.00
FS5	150±0.00	3564±0.67
FS6	186±0.00	3815±0.15
FS7	188±0.50	4156±0.00
FS8	270±0.34	4330±0.23
FH9	204±0.34	3640±0.34
FH10	270±0.34	3900±0.12
FH11	294±0.50	4276±0.26
FH12	300±0.00	4430±0.00

Table 4: Drug content % values of FC1-FH12

Formulation code	Drug content ±SD (n=3)	
	At 233nm	At 423nm
FC1	86.03±0.4	86.1±0.00
FC2	97.06±0.11	87.4±0.06
FC3	87.1±0.14	91.8±0.03
FC4	99.5±0.00	98.35±0.00
FS5	96.1±0.31	93.90±0.01
FS6	86.8±0.14	87.3±0.07
FS7	85.3±0.00	92.7±0.00
FS8	86.4±0.01	91.5±0.02
FH9	80.9±0.011	84.55±0.02
FH10	91.6±0.00	90.5±0.03
FH11	99.2±0.20	80.7±0.01
FH12	86.0±0.41	87.5±0.01

SD=standard deviation(mean), n=3

Table 5: Evaluation of prepared *in situ* gels

Formulation code	Physical appearance	pH ± SD	Gelling temperature (ºC) ± SD	Gelling time (sec) ± SD	Mucoadhesive potency(dyne/cm²) ± SD
FC1	Clear solution	4.99±0.03	36.0±0.01	56±0.6	1423.96±10.18
FC2	Clear solution	5.95±0.00	34.0±0.00	42±0.6	1917.68±0.00
FC3	Clear solution	5.20±0.02	33.0±0.02	39±0.0	2499.01±15.62
FC4	Clear solution	5.39±0.00	32.0±0.03	33±0.3	2692.02±15.59
FS5	Clear solution	5.04±0.01	44.0±0.08	59±1.0	1715.00±0.00
FS6	Clear solution	6.01±0.02	42.0±0.03	47±0.6	1934.31±3.12
FS7	Clear solution	4.71±0.013	30.0±0.07	41±1.0	2213.90±0.00
FS8	Clear solution	6.08±0.03	26.0±0.04	36±0.7	2504.93±15.59
FH9	Clear solution	6.15±0.00	40.0±0.02	58±1.3	1751.37±15.59
FH10	Clear solution	4.98±0.021	36.0±0.06	43±0.6	2026.81±0.00
FH11	Clear solution	4.55±0.003	30.0±0.01	40±0.0	2359.93±29.62
FH12	Clear solution	5.20±0.011	28.0±0.07	35±0.3	2530.90±15.6

SD=standard deviation(mean), n=3

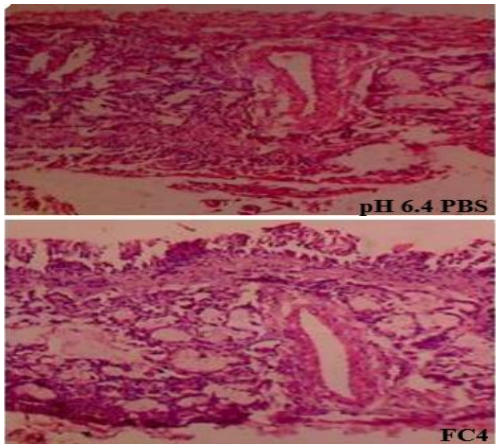

Figure 8: Histopathological studies of Goat nasal mucosa

***Ex vivo* Drug release profile**

Table 6: *Ex vivo* drug release data of Nasal *in situ* gels at 233nm

Time (Hrs)	% Cumulative drug release at 233nm											
	FC1	FC2	FC3	FC4	FS5	FS6	FS7	FS8	FH9	FH10	FH11	FH12
0	0	0	0	0	0	0	0	0	0	0	0	0
0.5	20.68	19.31	22.15	22.53	15.4	19.12	17.5	21.96	18.68	20.78	22.4	22.5
1	33.15	35.81	38.53	43.68	26.93	32.84	35	41.87	32.68	43.68	43.81	44.37
2	47.53	47.53	54.75	55.84	42.28	52.31	49.68	52.18	46.84	55.65	55.46	55
3	58.25	59.31	65.06	67.06	59.4	61.28	65.68	66.31	58.21	65.62	66.25	63.75
4	76.68	79.35	84.75	88.5	75.9	79.5	86.32	89.28	86.62	85.53	85.5	82.5
5	84.82	87.11	89.96	91.68	86.1	89.29	92.25	94.46	92.28	91.5	90.75	89.25
6	93.18	93.37	94.8	99.3	92.13	95.28	96.15	98.66	95.25	96	96.78	99

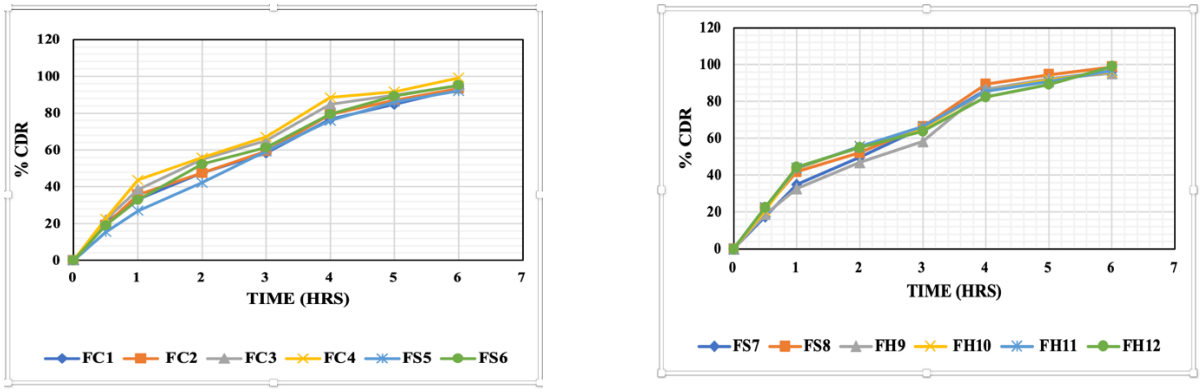

Figure 9: *Ex vivo* drug release data of Nasal *in situ* gels (FC1-FH12) at 233nm

Table 7: *Ex vivo* drug release data of Nasal *in situ* gels at 423nm

Time (Hrs)	% Cumulative drug release at 423nm											
	FC1	FC2	FC3	FC4	FS5	FS6	FS7	FS8	FH9	FH10	FH11	FH12
0	0	0	0	0	0	0	0	0	0	0	0	0
0.5	11.79	15.23	12.81	15.7	11.56	12.34	15.39	15.62	12.18	13.2	14.84	15.54
1	20.7	22.96	20.07	25.54	15.46	18.82	18.82	24.6	21.17	23.28	23.98	24.92
2	23.28	29.76	27.26	37.42	25.85	30.7	23.82	30.07	26.09	31.48	31.09	31.25
3	32.5	40.85	45.78	51.25	47.73	46.64	31.32	42.57	42.1	49.6	48.95	48.51
4	52.5	62.26	65.15	72.96	70.39	68.67	56.25	54.92	58.67	67.18	66.01	70.46
5	72.15	89.45	85.7	87.57	86.87	85.23	84.6	85.07	86.17	88.2	87.26	88.75
6	97.42	96.67	99.21	99.76	97.81	98.04	96.79	99.14	97.26	98.43	99.06	99.37

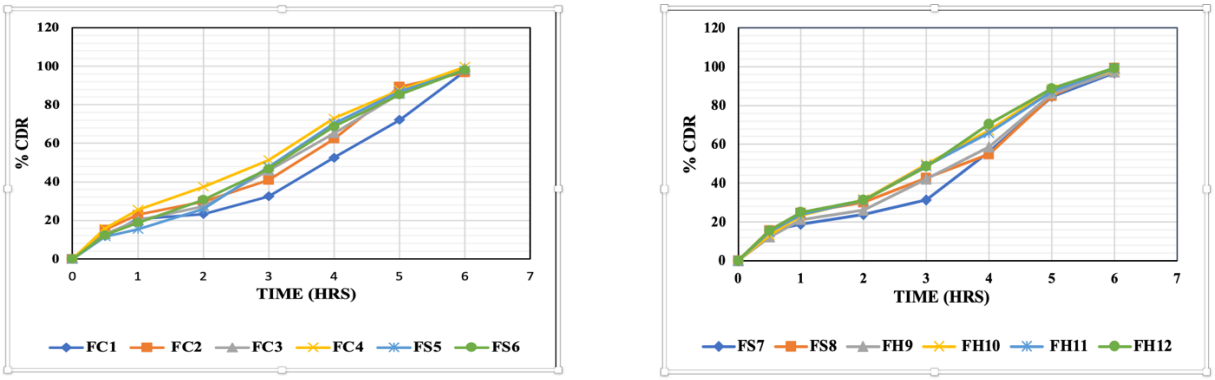

Figure 10: *Ex vivo* drug release data of Nasal *in situ* gels (FC1-FH12) at 423nm

Table 8: Stability studies of optimized formulation FC4

S.no.	Evaluation Parameters		Initial month	First month	Second month	Third month
1	pH		5.39±0.00	5.40±0.00	5.39±0.03	5.41±0.20
2	Viscosity(cp)	233nm	578±0.34	577±0.15	578±0.00	578±0.21
		423nm	4530±0.00	4530±0.02	4531±0.00	4530±0.01
3	Drug content(%)	233nm	99.50±0.00	99.60±0.11	99.54±0.32	99.50±0.00
		423nm	98.35±0.00	98.50±0.00	98.35±0.02	98.41±0.24
4	Mucoadhesive strength (dyne/cm²)		2692.02±15.59	2692.00±15.56	2692.50±0.00	2692.02±0.00
5	*Ex vivo* Drug release(%)	233nm	99.30±0.00	99.34±0.21	99.31±0.14	99.30±0.16
		423nm	99.76±0.00	99.70±0.00	99.76±0.03	99.75±0.10

DISCUSSION

Twelve formulations(FC1-FH12) were prepared by cold method by utilising a thermoreversible polymer(Poloxamer P188) and mucoadhesive polymers(Sodium alginate, Carbopol 940, HPMC K100) in varying proportions. The drug contents of formulated gels were measured by UV-Vis spectrophotometer in the range of 200-800 nm and the maximum absorbance was found to be at 233 nm for Metformin and Curcumin at 423 nm.

All preparations were subjected to quality control evaluation i.e., mucoadhesive potency, viscosity, gelation time and temperature and drug release profile.

The viscosity for 12 formulations varies from 150cp-578cp at 4ºC and 2850cp-4530cp at 37ºC due to increase in concentration of polymers. FC4 has the maximum viscosity at both temperatures.

The gelation temperature of all preparation was ranges from 26ºC- 44ºC and FC4 showed the suitable temperature of gelation among all preparations.

The gelation time of all formulations were in between 33 sec-58 sec and FC4 showed least gelation time.
Drug content percentage was determined for all the formulated nasal *in situ* gels and was observed in the range of 80.9% - 99.5% w/v at 233nm and 80.7% - 98.35% w/v at 423nm. Formulation FC4 has the highest % drug content.

The mucoadhesive potency of all the preparations were ranges from 1423.96 dyne/cm² to 2692.02 dyne/cm². The formulation FC4 showed the maximum force of detachment.

The *ex vivo* drug release of preparation FC4 was the maximum which was 99.3% at 233nm and 99.76% at 423 nm.

According to results obtained from tests FC4 was an optimized formulation.

CONCLUSION

The present work successfully formulated the thermoreversible *in situ* gel via nasal route of combination of Metformin and Curcumin which is an innovative approach for the targeted drug delivery to brain via olfactory region to treat Alzheimer's disease induced by type 2 diabetes in elderly population and evaluated for *in vitro* quality control parameters. The *in situ* gels was prepared by cold method with Poloxamer P188 and bioadhesive agents in altered concentrations. The formulation FC4 has been deliberated as an optimized formula as it has displayed the satisfactory Mucoadhesive strength, Rheological property, good Gelation temperature and time, *ex vivo* % Drug release. As there are no marketed products available, the prepared thermoreversible nasal *in situ* gel containing combined Metformin and Curcumin proves to be new area of drug delivery system in future and therapeutics for Alzheimer's disease.

ACKNOWLEDGEMENT

The author is obliged to Aurobindo Pharma Pvt. Ltd., Hyderabad for supplying the drug (Metformin) as gift sample and also obliged to CMR College Of Pharmacy, Hyderabad for granting the necessary facilities to execute our research work.

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Cite this article as:

Anuja Anku *et al*. Combination of metformin and curcumin thermoreversible nasal in situ gel formulation and In vitro-Ex vivo evaluation for diabetes-induced Alzheimer's disease. Int. Res. J. Pharm. 2021;12(6):26-34.
http://dx.doi.org/10.7897/2230-8407.1206140

Source of support: Nil, Conflict of interest: None Declared

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