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Preparation and Evaluation of oil Entrapped Gastro-Retentive Floating Gel Beads of Ondansetron HCL as Anti-Emetic

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Abstract:

The goal of the presented work was to create a gastro-retentive floating gel beads of Ondansetron HCL. Ondansetron is a selective 5-HT3 serotonin-receptor antagonist used for its antiemetic properties. It is one of the four FDA-approved 5-HT3 serotonin-receptor antagonists used to combat nausea and vomiting. It is metabolised by first pass effect in liver which drastically reduces its systemic availability. This formulation aimed to improve drug's bioavailability by prolonging its release for up to 12 hrs and thus its gastric retention. A total of 6 formulations were prepared. The emulsion gelation method was used to formulate these oil entrapped floating drug beads. Each of the formulations prepared were assessed for a number of factors i.e. morphology, floating behaviour, drug content, in vitro % cumulative drug release (%CDR). The physicochemical properties of the produced micro gel beads were found to be satisfactory. Also each of the formulated batch demonstrated satisfactory buoyancy in virto profile. Ondansetron 8 mg Slow Release Capsules from Bayview Pharmacy was taken as the standard. To compare the selected optimized formulation (F4) with the regular marketed formulation, various model dependent release kinetics were used including zero and first order, models. The results showed highest data fitting to the equation of zero order model for the formulation F4 (with R^2 = 0.9948), which indicated that the drug release followed non-Fickian diffusion mechanism.

Keywords **—Ondansetron HCL, gastro retentive, FDDS, Sodium alginate, model dependent release kinetics.**

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I. INTRODUCTION

The fact that uniform absorption is not exhibited by all the medications across the entire gut or gastrointestinal tract (GIT) pose a significant barrier in oral controlled delivery of thesedrugs. Conventional controlled oral dose formulations exhibit two key challenges i.e. the erratic emptying time from gut (GET) and brief time of gastric retention (GRT). Medication system intended for gastro retentive delivery are deviced to have extended stay time in stomach/ gut. Thereby gradually releasing their content continuously in upper jejunum andduodenum part of GIT resulting in desired persistent effect (1–4). An extended duration of stomach residence is especially desired for the drugs that are local acting, are particularly absorbed from the upper small intestine or stomach, are highly degradable in colonic condition or are poorly soluble in acidic pH of the gut (5–7).

Agent blocking 5-HT3 serotonin receptor, OndansetronHCLworks on the 5-HT3 receptors that can be found at the vagus nerve terminals. The vagus nerve can sense nausea and vomiting triggers within the GI tract, such as stomach irritants. It forms synapses within the nucleus tractussolitarius of the brainstem, another region important in vomiting. The peripheral actions of ondansetron are

thought to be the predominant mechanism for its antiemetic effects(8). Multiple dosing is required to be given for OndansetronHCL in order to maintain wanted systemic concentration responsible for desired therapeutic outcome which helps improving compliance of sufferer. This is so because the half-life of approximately 3 to 4 hrs has been reported for OndansetronHCL which results only in 12% of oral absolutebioavailability(9-12). Also, attributed to this, OndansetronHCL has been reported to be particularly absorbed from the jejunum andduodenum part of gut where it strongly directly correlates with the available dosage (13,14). Additionally, at all physiological pH values, OndansetronHCL has been shown to be very soluble with 157 mg per ml in 5.5 pH water and 183 mg per ml in 1.0 pH solution of HCl of strength 0.1 mol per lt. (15,16). This therefore suggests it to be a good choice for designing gastro retentive delivery system (17,16).

Number of methods are being employed to preparing effective delivery system with gastro retention. Among them, the floating forms embedded with drugs are most widely used technique (20). The bulk density of these drug carrying floating delivery systems (FDDS) is quite low in comparison to that of the gastric fluids. Therefore, they remain suspended over these fluids in the gut for extended time period without slowing down or altering their emptying rate. During this time period, the medications are gradually freed at the desired location in a controlled manner. Once the FDDS has released all the drug content the leftover is removed along with gastric emptying. As a consequence, with prolonged stay in gut, the variation in desired therapeutic concentration of active agent in plasma also gets controlled (21,22).

Looking into some of the previously reported studies on the formulation and then analysis of this gastro retentive systems, Khalaf. et. al. created a matrix tablets employing sodium carboxymethyl cellulose (CMC), guar gum and hydroxypropyl methylcellulose (HPMC), as polymers. They developed formulations both separately and in combination of these polymers. They reported increase in duration of stomach residency and there by the boosted bioavailability of the drug (23). Likewise, Patel et al.(24)prepared a FDDS using psyllium huskand Natural gum. They employed HPMC for gel matrix creation. In another work, a bioadhesive systemfor controlled releaseorally was prepared and studied byKarosiya. They used different polumers i.e. Ethyl cellulose, HPMC and Sodium CMC (20). In similar line, Waniand his group (25), formulated and assayed an effervescent FDDS system using several different polymers.

In the work elaborated in the presented research article, a novel formulation of floating gastro retentive OndansetronHCL gel beads were formulated, evaluated and also compared with the marketed analogue for its controlled release efficiency. Here 5 different polymers in varying concentrations were used. The resulting preparation consisted of a system of multiple units of OndansetronHCL appearing as an assembly of gel beads exhibiting controlled release of drug agent. Each individual small and free flowing bead thus were an independent delivery units able to release OndansetronHCLuninterruptedly in the intended interval of dosing. Thus the study has effectively designed a dependable multi-unit floating delivery dosage of OndansetronHCLimbibing all the benefits of single-unit floating system eliminating its drawbacks like adhering to or getting clogged in the gut etc. (26,27).

II. EXPERIMENTAL:

Materials:

OndansetronHCLwas received as a sample from Sun Pharma Pvt, Ltd., Ahemadabad, India. Sodium Alginate and Pectin was purchased from Arora & co., Delhi, India. Other polymers were purchased from Central Drug House (P) ltd., New Delhi, India. All the other chemicals used were of analytical Research grade.

Methods:

The drug procured was identified and characterised using UV and FTIR. Loss on drying, melting point, solubility and partition coefficient were also determined using standard procedures as described in pharmacopoeias.

1. Calibration curve of Ondansetron HCL in phosphate buffer solution (pH 7.4) and water:

Working standardsolutions of OndansetronHCL pure sample in 10-30 µg/mlrange ofconcentration were obtained by properly diluting with phosphate buffer solution of 7.4 pH and absolute water of the primary stock solutions. Further, calibration curves were used to determine the concentration of OndansetronHCL present in the microspheres(28).

2. Drug-Polymer compatibility study:

In order to determine the chances of potential reactions among the excipients used and the active drug OndansetronHCL, in the formulations prepared, compatibility tests were performed. For this, physical mixes containing the medication and different excipients, were separately prepared in 1:1 ratio. The possible interaction between the drug and the excipients were studied by Infra-red spectroscopy between 1000 to 3500 cm^{-1}. The samples (10 mg per vials) were kept at 50°C for 15 days and in the same quantity immediate samples were taken and both compared for the compatibility.

3. Preparation of Floating gel beads of Ondansetron HCL:

Various formulations were designed using sodium alginate along with soybean oil with different concentrations of polymers. The polymers used was Pectin. Total 6 formulations were formulated, depending on the polymer concentrations. All the formulations were prepared by the emulsion gelation method. In this technique, polymer is dissolved in water with stirring. Then oil is added to the resulting polymer solution with continuousagitation to form an emulsion to which then the drug is added. This obtained homogenized solution mixture is then extruded into calcium chloride solution with gentle agitation at room temperature which results in the formation of drug loaded gel beads. The formed beads were filtered, washed and dried**.**Complete formulation design for 20ml of each formulation samples (made so with distilled water quantum sufficit or Q.S.) is shown in table 1 below.

Table 1 Different Formulation Design

S.No.	Ingredient(% w/w)	F1	F2	F3	F4	F5	F6
1	Ondansetron HCL	1	1	1	1	1	1
2	Sodium alginate	0.9	0.8	0.7	0.45	0.4	0.35
3	Pectin	0.1	0.2	0.3	0.05	0.1	0.15
4	Soyabean oil	3	3	3	3	3	3
5	Distilled water	q.s	q.s	q.s	q.s	q.s	q.s

Evaluation and Characterization of Floating Gel Beads Formulations:

4. Study of size and morphology of emulsion gel beads:

The diameter of beads was determined by screw gauge. For this purpose, 20 dried beads were randomly selected from each batch and the mean diameter was determined by screw gauge. The least count of screw gauge was 0.005 mm. Colour and shape of dried beads of each batch was also recorded.

5. Floating time of emulsion gel beads:

The gel bead samples (n=10) were placed in a beaker filled with 50 ml of 0.1 N HCl solution. Temperature was maintained at 37^0C. The floating time of beads was observed for 20 hrs. The preparation was considered to have buoyancy in the test solution only when all the gel beads floated in it(29).

6. Determination of drug content:

50 mg of beads were weighed and crushed in pastel mortar.The crushed material was dissolved in 25 ml of phosphate buffer (pH 7.4). Volume of this solution was made up to 50 ml with washings of mortar. This solution was shaken with the help of wrist action shaking machine for 5 hrs and then kept for 24 hrs. It was then filtered. The filtrate was assayed by spectrophotometry at 222 nm. The drug content and the encapsulation efficiencies were determined(30,31).

7. Drug release studies:

The dissolution of Ondansetron HCL sodium alginate beads was studied using USP Type II

dissolution apparatus (Electolab, E80) containing 900 ml of phosphate buffer (PSB) at pH 7.4 and water maintained at 37±0.5^{0}C and stirred at 50 rpm. Samples were collected periodically and replaced with fresh dissolution medium. These samples were analysed for the drug present in them with the help of UV spectrophotometer (UV- 1700, Pharmaspec, Shimadzu). Only batches with good drug content were selected for the release study. The cumulative % drug release was calculated using standard calibration curve.

8. Swelling studies:

Beads were studied for swelling characteristics. Only the batches with good drug content and entrapment efficiency were selected. Samples from drug-loaded beads were taken, weighed and placed in a wired basket of USP dissolution apparatus II. The basket containing beads was put in a beaker containing 100 ml of 0.1 N HCl (pH 1.2) maintained at 37°C. The beads were periodically removed at predetermined intervals and weighed. Then the swelling ratio was calculated as per the following formula (32):

Swelling ratio = weight of wet beads/weight of dried beads

Further Study:

Based on the results obtained from the 6 formulations above, 1 formulation was taken for further evaluation. These were formulation number F4, now denoted as selected Final formulae (FF). Fresh formulation of the selected formulations was prepared and evaluated for above listed parameters.

This compared with the available marketed preparation (Ondansetron 8 mg Slow Release Capsules from Bayview Pharmacy which is an extended release formulation) for the evaluation parameters, release kinetics, similarity factor and difference factor.

Kinetic Modeling:

The mechanism of Ondansetron HCL release from the floating gel beads was studied by fitting the dissolution data of optimized formulation in following methods of zero and first order models.

Zero Order Model: Qt = Qo + Kot

First Order Model: log C = log Co – Kt/2.303

Where, Ko was release rate constants, Q/Qo was fraction of drug released at time t, K was a constant and n was diffusion constant that indicates general operating release mechanism. For Fickian (diffusion controlled), n ≤ 0.5; for non Fickian release, 'n' value is in between 0.5 to 1.0; for zero order release, n=1; for super case transport II, n > 1.040. Based on the slope and the r2 values obtained from the above models the mechanism of drug release was decided.

III. RESULT AND DISCUSSION

1. *Physical characterization of the Drug:*

Ondansetron HCL was white, odourless and bitter tasting with UV absorbance at 222 nm. Various Characterization outcomes are list in table 2 under:

Table 2: Results of Characterization of Ondansetron HCL

S.no.	Properties	Standard value	Observed value
1.	Appearance	White powder	A whity powder
2.	% Loss on drying	NMT 0.2 % w/w	0.18 % w/w
3.	Melting point	178.5°C to 179.5°C	179°C
4.	Solubility	Determined in distilled water, pH 7.4 phosphate buffer	freely soluble in phosphate buffer (77.23 mg/ml), sparingly soluble in water (54.26 mg/ml)
5.	Partition Coefficient	1.62	1.60

2. *Standard Calibration curve of Ondansetron HCL:*

Samples prepared in phosphate buffer pH and water, average (shown in table 3) was considered to draw the calibration curve at 222 nm. Fig. 1 shows the standard calibration curve with a regression value of 0.9995, slope of 0.0217 and intercepts of 0.01. The curve was found to be linear in the concentration range of 10-30 µg/ml.

Table 3: Standard graph of Ondansetron HCL

Concentration (µg/ml)	Absorbance (at 310nm)
0	0
5	0.121
10	0.225
15	0.334
20	0.439
25	0.546

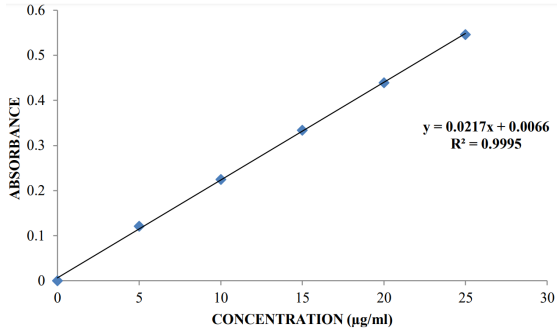

Fig 1: Standard calibration curve of Ondansetron HCL

3. *Drug-Polymer compatibility study:*

The FT-IR spectra of the formulations were compared with the FTIR spectra of the pure drug, immediately and after 15 days (when kept at 50^0C). The peaks obtained in the spectra of each formulation correlated with the peaks of standard pure drug spectrum. It did not show any well-defined reactions among the drug, Ondansetron HCL and various excipients. This indicated that the drug is compatible with the formulation components i.e. no chemical reaction occurs between polymers and the drug in samples. The spectra for pure drug, drug-excipients mixture and optimized formulation are shown in Figures 2-4.

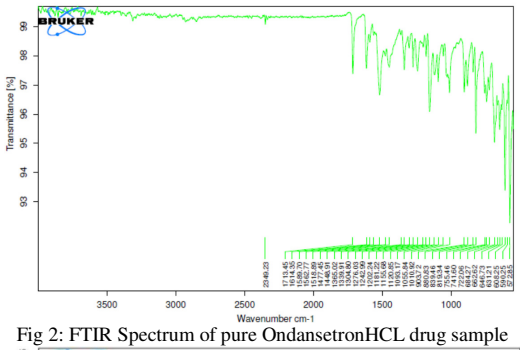

Fig 2: FTIR Spectrum of pure OndansetronHCL drug sample

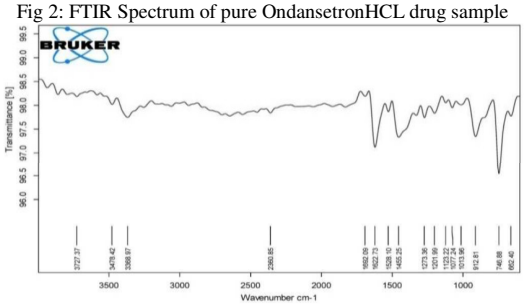

Fig. 3: FTIR spectrum of ondansetron HCL with Sodium alginate

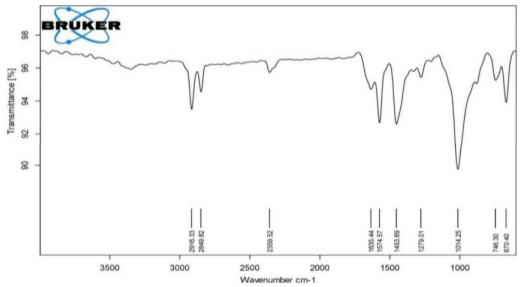

Fig.4: FTIR spectrum of ondansetron HCL with Pectin

4. *Evaluation and Characterisation of Floating Gel Beads Formulations:*

Each of the formulations were found to contain spherical white gel beads with regular shape and size in range of 1.06-1.52mm. The floating lag time was found ranging from 6-61 min, with 6 to 8 min being for formulation F4 and 41 to 61 min being for the formulation F3. The floating time was almost 10 hours for all the 6 formulations. The drug content was highest in formulation F4 i.e. 99.81% while all other formulations also showed significant score for drug content.

5. *In vitro Drug Release:*

Cumulative Drug Release of Ondansetron HCL in PSB pH 7.4 in 12 hrs was found to be 98.82% and 89.12% in water for the formulation F4, which was highest among all the 6 formulations. Also, between water and PSB, the dissolution study showed highest % cumulative drug release when the medium was PSB (pH 7.4).

Based on this data, it was found that formulations F4, could be considered the selected formulation with desirable flag, for further study.

6. *Swelling ratio:*

The swelling ratio was recorded at different time points i.e. 0, 20, 40, 60, 80, 100, 120, 140, 160, 180 minutes. All the observations were taken and arranged in a plot to get an idea about the trend of swelling ratio with respect to time. F4 was found to have highest value of swelling ratio i.e. 1.36% among the 6 formulations enlisted in table 4 and shown in figure 5.

Table 4 Swelling Index of the Selected Formulations at different times

Batch code	Tim								
	20	40	60	80	100	120	140	160	180
F1	1.13	1.11	1.18	1.18	1.18	1.18	1.08	1.08	1.08
F2	1.15	1.16	1.15	1.16	1.16	1.16	1.14	1.14	1.14
F3	1.12	1.13	1.13	1.14	1.15	1.15	1.13	1.13	1.15
F4	1.36	1.39	1.36	1.35	1.36	1.36	1.36	1.36	1.36
F5	1.13	1.12	1.12	1.11	1.14	1.14	1.12	1.12	1.14
F6	1.19	1.18	1.19	1.18	1.17	1.17	1.18	1.18	1.18

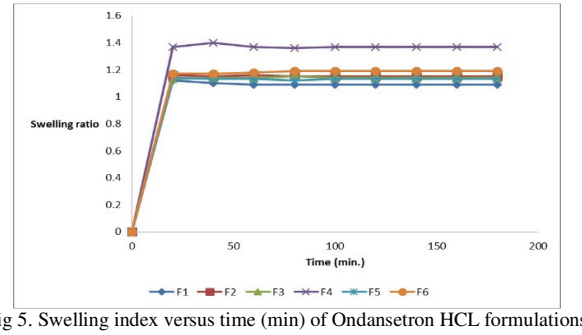

Fig 5. Swelling index versus time (min) of Ondansetron HCL formulations

7. *Comparative study of the Final Formulation with Marketed Ondansetron:*

The drug content in marketed formulation was found to be 99.13% which is very good. The drug was 91.21% released in 12 hours it means the formulation's release is sustained.The plot of cumulative percent drug release v/s time for the selected final formulation (FF) and Ondansetron HCL (MF) is plotted in Fig 6.

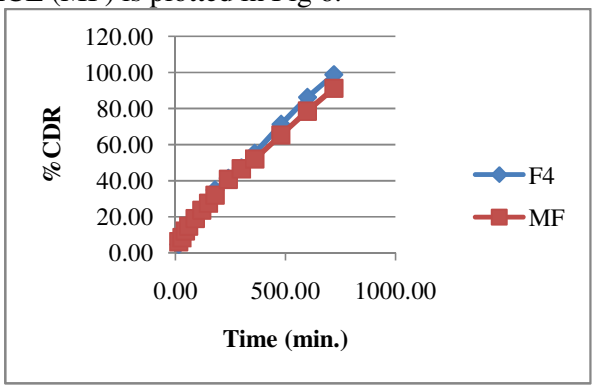

Fig 6. Cumulative percent drug release v/s time for FF and Ondansetron HCL MF

8. *In Vitro Drug Release Mathematical Kinetics Study Models:*

Model Zero and First Order Methods

The data obtained from in vitro dissolution studies were fitted to zero-order, first-order, equations. The dissolution data obtained were plotted as time versus cumulative % drug released for zero order kinetics, as time versus log cumulative % drug remaining for First order release kinetics models. The Release Kinetics of Final Formulation (FF) and the marketed formulation (MF) are compiled in table 5 under. The plot has been shown in figure 7 (for zero order kinetics) and figure 8 (for first order kinetics).

Table 5 Release Kinetics of Final Formulation (FF) and the marketed formulation (MF)

Time	Final Formulation		Marketed Formulation	
	% cdr	log % cdr remaining	% cdr	Log % cdr remaining
15	5.62	1.9846	6.32	1.9821
30	8.22	1.9721	8.48	1.9717
45	11.72	1.9352	12.42	1.9334
60	13.56	1.9262	14.77	1.9203
90	17.37	1.9277	19.13	1.9184
120	22.81	1.8981	23.82	1.8924
150	28.26	1.8462	27.67	1.8701
180	34.72	1.8241	32.13	1.8423
240	41.46	1.7781	40.87	1.7826
300	47.16	1.7138	46.53	1.7472
360	55.16	1.6626	52.12	1.6908
480	71.23	1.4504	65.26	1.5298
600	86.16	1.1341	78.65	1.3113
720	98.82	0.1195	91.21	0.9283

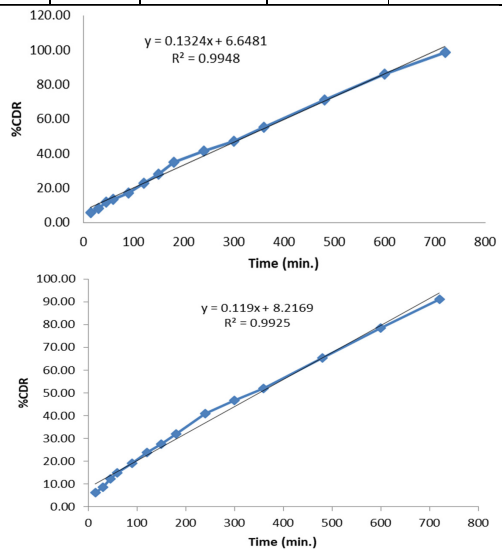

Fig. 11 Zero Order Kinetic Graph of: a) FF b) MF

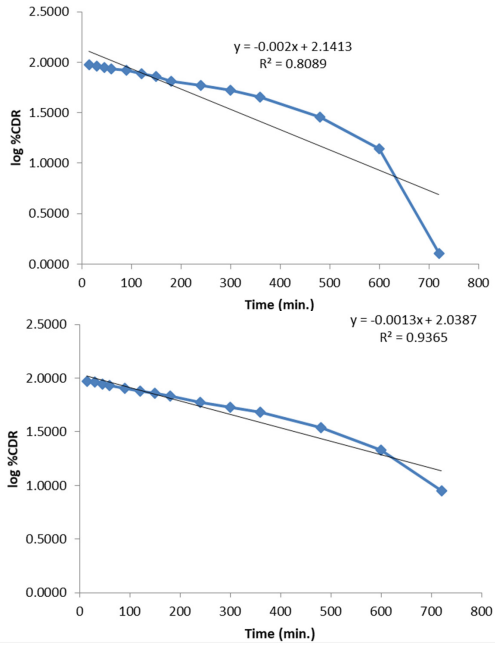

Fig. 12 First Order Kinetic Graph of: a) FF b) MF

R^2i.e the determination coefficient indicates the best fitting among all the kinetic models that are considered in these kind of study. Here, in present study it was with the Zero Order kinetic model, that highest coefficient of determination value (R^2 = 0.9948) was achieved for the formulations. Thus adherence to this kinetic model thereby suggested the conclusion that drug release mechanism followed diffusion which also has been reported as competent to gel based systems.

IV. CONCLUSION:

With the aim to improve Ondansetron HCL's oral bioavailability by controlling and extending the medication dosage release, the presented study made a commendable effort in formulating the floating gel beads as part of FDDS. Further it was found to be in compliance with study profile of Marketed Ondansetron, the marketed extended release formulation of Ondansetron HCL. Based on the findings of the experimental outcomes of FT-IR study, lacking significant shift in absorbance peaks of formulations vs the pure drug, drug stability in gel beads can be confirmed. Various Polymers like sodium alginate, pectin, can be used to formulate a floating gel beads which are reported to be Biocompatible. All the formulations containing an optimum polymer concentration exhibited maximum drug release in a period of 12 hrs. Considerable reduction in % cumulative release of Ondansetron HCL was seen as the concentrations of polymers hiked. The overall curve fitting into various mathematical models was found to be acceptable. The Final formulation (F4) best fitted into kinetic models indicating the mechanism of drug release to have observed the effect of diffusion for sustained drug release. Thus, the formulated floating gel beads seem to be a potential candidate as an oral gastro retentive controlled drug delivery system in prolonging the drug retention in stomach and increasing the bioavailability of drug over the conventional drug delivery systems. Further, in future various stability studies can be performed along with in vivo studies to support the hypothesis.

CONFLICT OF INTEREST

There is no conflict of interests as declared by all the contributing authors.

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This Review article has been compiled with equal contributions from all the authors and thereafter approved for the publication. All authors have reviewed and thereafter approved the final manuscript.

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