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Development and *in vitro* evaluation of effervescent floating matrix tablet of neritinib: An anticancer drug

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Abstract: Neratinib is a potent anticancer drug, used for the treatment of breast cancer. It is poorly soluble at higher pH, which tends to minimize the therapeutic effects in the lower GIT leads to its poor bioavailability. An attempt has been made to prepare and develop a novel gastro-retentive system of neratinib to improve the drug bioavailability in the GIT by enhancing the gastric retention time. The floating matrix tablets were prepared by various proportions of carbopol 940, micro-crystalline cellulose (MCC) and ethyl cellulose (EC), sodium bicarbonate ($NaHCO_3$) as gas forming agent, by direct compression. The formulation mixture was assessed for pre and post compression test, lag time, *in-vitro* floating, FTIR, water uptake/swelling index, *in vitro* and kinetic release studies. The findings revealed that, the parameters of compression (pre and post) were within USP limits. The floating tablets swelled well and floated for more than 24h, with less than 120 seconds of buoyancy lag time. The optimized formulation F3 showed sustained release up to 12h; a non-Fickian mechanism. Therefore, all the results and findings have shown that developed neratinib floating matrix system is a promising approach as a drug delivery system and application in the treatment of breast cancer.

Keywords: Neratinib, carbopol, effervescent floating tablet, *in vitro* drug release, release kinetic.

INTRODUCTION

Cancer is considered the leading public health problem and major cause of death. The number of cancer cases which were detected in 2008 is 7.6 million and estimated 18.1 million in 2018 in the world. (Bray F *et al*., 2018). Every year there is an enormous increase in cancer cases. The commonest cancers are lung and breast cancer each contributing 12.3% worldwide. In women, the total number of diagnosed cancer cases in 2018 is 8,218,216, in which breast cancer cases are almost 3 million, contributing to 25.4%. It is the second most widespread cancer and the main reason of death. The frequency rates of breast cancer vary almost four-fold across the world's different regions. Based on the data from the Association of Central Cancer Registries of North America and the National Program of Cancer Registries (NPCR) the cancer cases estimate overall are 1,735,350. Therefore, more than 4,700 new cancer cases are diagnosed per day were diagnosed in 2018 (Rebecca *et al*., 2018). Anti-cancer or anti-neoplastic drugs currently account for about 4.2% of the total sales of the world pharmaceutical market. Total world sales of ant-cancer drugs are over 400 million US dollars, it is likely to cross 10 billion U.S. dollars in the next 3 years (Siegel *et al*., 2017).

A number of drug delivery systems are available to improve poor bioavailability of drugs in the upper part of the GIT (Chen *et al*., 2013), such as microspheres (Qiufang *et al*., 2018), nanoparticles (Pallabita C *et al*., 2018; Jain *et al*., 2016), B-cyclodextrin complex (Yallapu *et al*, 2010), nanofibre (Malik *et al*., 2015) and gastroretentive drug delivery system (GRDDS) etc. Floating drug delivery system (FDDS) was found to be the most important category of gastroretentive drug delivery system. Which extends the gastric residence time (GRT) in the stomach with no effect on the gastric emptying time (GET) for an extended time period. This delivery allows sustained release of drug in the stomach and upper part of the GIT (Lopes *et al*., 2016; Gangadharappa *et al*., 2010). The GRT can be attained by various mechanisms like bioadhesion, flotation, ion exchange resins, swellable and expansion systems, erosion systems, modified shape systems, high density systems, raft forming systems superporous hydrogels and low density systems (Mohamed Rahamathulla *et al*., 2019; Davis *et al*., 1986; El-Said *et al*., 2016; Kumar M *et al*., 2018).

Neratinib is a potent anti-cancer drug, used for breast cancer which is newly approved by the US FDA in July 2017 (US FDA, 2017). It is a protein kinase inhibitors, member of the 4-anilino quinolidine. It is an irreversible inhibitor of tyrosine kinases receptor human epidermal growth factor receptor 2 with potential anti-tumor activity (Yi-fan *et al*., 2011; Burstein *et al*., 2010; Iqbal *et al*., 2014). Neratinib exhibits poor aqueous solubility, extremely low oral bioavailability in higher pH which tends to minimize the therapeutic effects (Feldinger *et al*., 2015). To overcome this, the challenge is to develop an oral floating drug delivery system which sustained the drug release in the upper part of the gastrointestinal tract (GIT) for a prolonged time period. Based on the literature survey, no research work was reported for neratinib

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delivery using carbopol and microcrystalline cellulose by effervescent technique. Which makes the present research work novel in existing FDDS. The objective of the present research was to design and develop a promising neratinib floating effervescent matrix tablet by carbopol, microcrystalline cellulose and ethyl cellulose. The feasibility and effect on drug release of the various proportion of microcrystalline cellulose and ethyl cellulose with carbopol were investigated. The pre and post-compression tests, lag time, water uptake studies, total buoyancy time and in-vitro release behaviour of developed formulations with the drug release kinetics and its mechanisms were also evaluated.

MATERIALS AND METHODS

Materials

Neratinib (NTB) purchased from Beijing Mesochem Technology Co., Ltd. Beijing, China Carbopol 940 purchased from Acros Organics (Belgium), ethyl cellulose and microcrystalline cellulose (Avicel PH-101) purchased from Fluka Biochem (US) and magnesium stearate, lactose and sodium bicarbonate from Sigma Aldrich Chemie GmbH (Germany) respectively. All other ingredients and reagents used were of analytical grade.

Methods

Preparation of effervescent floating tablets

Various formulations of Floating matrix tablets (F1 to F5) were made by direct compression technique. Neratinib and other constituents were thoroughly mixed to achieve uniform-mixture before compression. Ingredients such as carbopol 940 and microcrystalline cellulose as the swellable polymer, ethylcellulose (EC), a release retardant, sodium bicarbonate as a gas generating/forming agent, a diluent as lactose and a lubricant magnesium stearate were utilized and formulation details are shown in table 1. Prior to compression, the powder mixture was assessed for micromeritic properties (pre-compression) such as the angle of repose (AOR), Hauser's ratio, bulk and tapped density, and Carr's index. Finally, powder mixture was compressed into tablets by single rotary punching (10 mm flat punches) machine (D-63150, Erweka AR 402, Germany).

Evaluation of Post-Compression Parameters

The post-compression parameters like friability (PTF20E, Pharma Tester, Germany), weight variation, drug content (DC) and unofficial tests like hardness, diameter, and thickness were evaluated. For DC test, 10 tablets were randomly picked and powdered in mortar, 40 mg equivalent of the drug was dissolved in methanol (10mL) and diluted to a suitable concentration. The absorbance was measured at a wavelength of 265 nm in UV-VIS spectro-UV-2550 (Shimadzu, Japan). The diameter, thickness and hardness of the tablet were measured using hardness tester (Erweka-TBH 125, Germany).

Drug excipients compatibility studies

Pure neratinib and optimized floating matrix tablet were characterized by FTIR Spectroscopy. In a mortar potassium bromide with optimized formulation (0.12%) were grounded into a fine powder. A thin transparent pellet was prepared by hydraulic pressure of 150kg/cm^2 at an ambient temperature. At 4000 to 500cm−1 wave number the samples were scanned (Model 4700, Thermo Fisher Scientific, and USA).

In-vitro floating studies (In vitro buoyancy)

In-vitro floating study was performed for all formulations. Randomly tablets were selected from each batch, and kept in a 100mL of glass beaker containing 0.1N HCl (dissolution medium) maintained at 37±0.5°C in the water bath. The tablet's time to arise to the surface of the dissolution medium in the beaker was aken as uoyancy lag time. Visually observed the duration of the tablet continuously float on the medium to be total buoyancy time.

Water uptake (WU) or swelling index studies (SI)

The WU is the ability of the tablet to take up water and swell. It was analysed by placing the previously weighted selected tablets in 900ml dissolution medium HCl buffers (pH1.2) in the basket (type-I.) at 37±0.5ºC for 12h. The tablets has been detached from the dissolution basket at the end of 12h. The excess water was detached with filter paper and weighed (Mohamed Rahamathulla *et al*., 2019). The experiment was performed in triplicate. The water uptake study was calculated by the formula:

$$\text{Water Uptake studies } \% = \frac{W_E - W_A}{W_A} \times 100$$

W_E= Weight of enlarged tablet, W_A= actual weight of tablet

In vitro drug release study

Using USP Dissolution Testing Apparatus 2 (Pharma test, D-63512 Hainburg, Germany), from the tablet formulations the drug release rate was determined. The dissolution test was performed for 12h at 37±0.5°C using 900 ml HCl buffer solution (pH 1.2) at 100 rpm. From the dissolution apparatus, a sample of 5ml was withdrawn for 12h at regular time intervals. In order to maintain the sink condition, a fresh dissolution medium was replenished for the withdrawn samples. By using membrane filter (0.45µ), the samples were filtered and diluted to an appropriate concentration. The solutions were determined at 265 nm by UV-Visible spectrophotometer (UV-2550, Shimadzu, Japan).

Drug release kinetics

To explain the drug release kinetics of neratinib floating tablet formulations several mathematical models were used. The release kinetics were fix by finding the best fit to the matrix (Higuchi), Hixson Crowell, Korsmeyer-Pappas, first order, and zero order plots.

Table 1: Composition of neratinib floating matrix tablets

Formulation No (FN)	F1	F2	F3	F4	F5
Neratinib (mg)	40	40	40	40	40
Carbopol 940 (mg)	20	40	60	80	80
Ethyl Cellulose (mg)	30	-	-	-	-
MCC (mg)	20	20	40	60	80
Sodium bicarbonate(mg)	40	40	40	40	40
Magnesium Stearate (mg)	3	3	3	3	3
Lactose (mg)	147	157	117	77	57
Total (mg)	300	300	300	300	300

Table 2: Pre-compression properties of matrix floating tablets (F1-F5)

F No	Tapped density* (g/cm3) ± SD*	Bulk density (g/cm3) ± SD*	Carr's index* (%) ± SD*	Hauser ratio	Angle of repose (°) ± SD*
F1	0.608±0.78	0.566±0.012	6.90± 0.92	1.07	27.02±0.29
F2	0.665±0.55	0.612±0.026	7.27±0.77	1.07	24.93±0.09
F3	0.612±0.28	0.527±0.058	13.88±1.29	1.16	21.80±0.37
F4	0.493±0.11	0.437±0.071	11.35±0.48	1.12	22.58±0.11
F5	0.445±0.19	0.392±0.073	11.91±.93	1.15	21.40±0.08

Table 3: Post-compression properties and evaluation of lag time and total buoyancy time of floating matrix tablets (F1-F5)

F No	Hardness (Kilogram) (mean ± SD*)	Drug content (%) (mean ± SD*)	Friability (%) (mean ± SD*)	Thickness mm (mean ± SD*)	Lag time (seconds)	Total buoyancy time (h)	% of swelling
F1	4.97 ± 0.11	97.98 ± 0.61	0.77 ± 0.02	3.97± 0.35	55	>24	128.66
F2	4.86 ± 0.24	98.47 ± 0.82	0.85 ± 0.05	3.95± 0.22	11	>24	161.66
F3	5.22 ± 0.13	100.59 ± 0.39	0.71 ± 0.07	3.95± 0.84	47	>24	180.09
F4	5.44 ± 0.21	100.06 ± 0.25	0.92 ± 0.03	3.99± 0.71	39	>24	357.23
F5	5.31 ± 0.19	99.25 ± 0.42	0.81 ± 0.08	3.98± 0.96	60	>24	348.15

*Standard deviation, n=3

STATISTICAL ANALYSIS

One-way analysis of variance (ANOVA) was used to analyse the *in vitro* dissolution rate of tablet formulations using IBM SPSS statistics V15 [USA].

RESULTS

Pre-compression parameters of powder mixture

From the powder mixture various pre-compression/ micromeritics parameters were evaluated for all formulation (F1-F5). Table 2 showed all pre-compression parameters evaluated. The tapped and bulk densities were in between 0.392 ±0.073 to 0.612 ±0.026g/cm^3 and 0.445±0.19 to 0.665±0.55g/cm^3 respectively.

Post-compression parameters of tablets

The tablet hardness was found to be approximately 5 kg/cm^2. The friability and thickness of the tablet were found to be below 1% and 4.0 mm respectively. Table 3 showed all the evaluated post-compression parameters of matrix floating tablet.

Drug excipients compatibility studies

The FT-IR spectra of pure neratinib and optimized formulation (F3) are shown in fig. 1.

In vitro buoyancy studies

Table 3 showed the floating lag time and total floating time of all formulations ranging from 16-57s and tablet without disintegration constantly buoyant for >24h. At different time intervals of the floating behaviour of the matrix tablet, the photographs had taken are presented in fig. 2.

Water uptake study (WU)

The WU by the polymers was determined for all the developed matrix floating tablets as shown in table 3. At the end of 12 h, all tablets achieved complete swelling.

In vitro dissolution studies

In-vitro dissolution studies were performed on floating matrix tablets of neratinib (F1-F5). Fig. 4, shows the in-vitro dissolution curve of neritinib floating tablets

Mechanism of drug release

Various models were fitted to in-*vitro* drug dissolution profiles and release data were analysed by PCP disso software. The R^2 (correlation coefficients) were employed to calculate the precision of the model. Table 4 shows the values n, k and R^2. For Hixson-Crowell, Korsmeyer-Peppas, first order models and Higuchi the R^2 values have been calculated and compared. The exponent(s) for diffusion (n) were from 0.3679 to 1.0803.

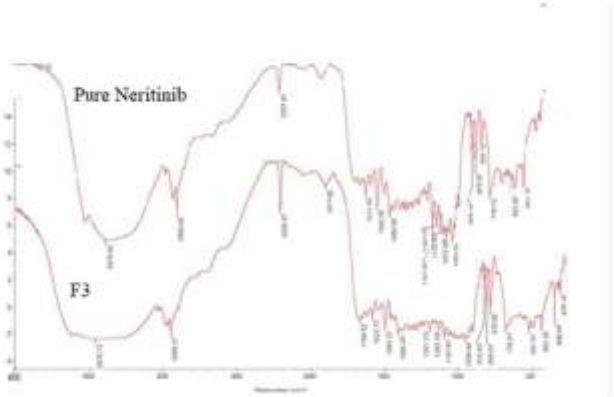

Fig. 1: FT-IR spectra of Pure Neratinib and optimized formulation (F3)

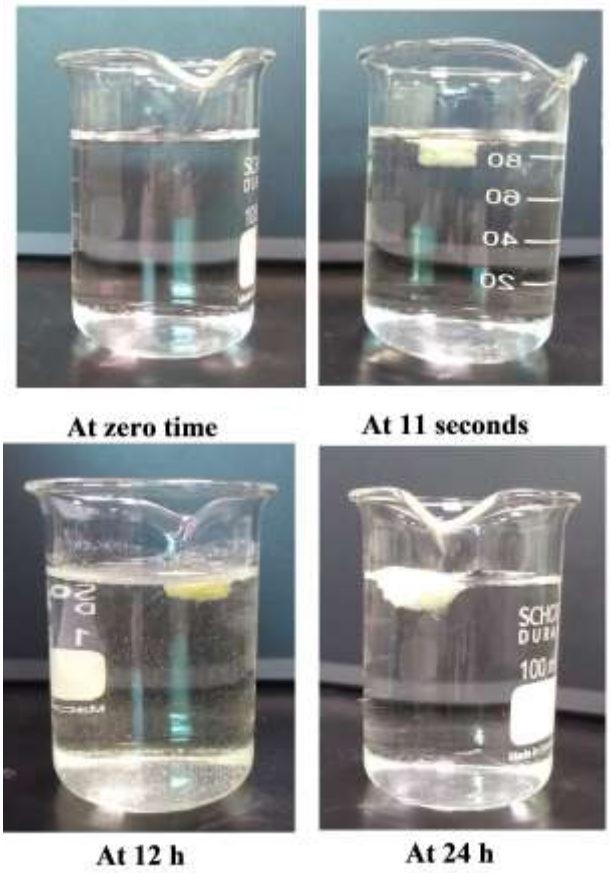

Fig. 2: Photographs of *in vitro* floating behaviour of floating tablet formulation (F3)

Fig. 3: Swelling profile of floating tablet formulation of Neratinib (F4)

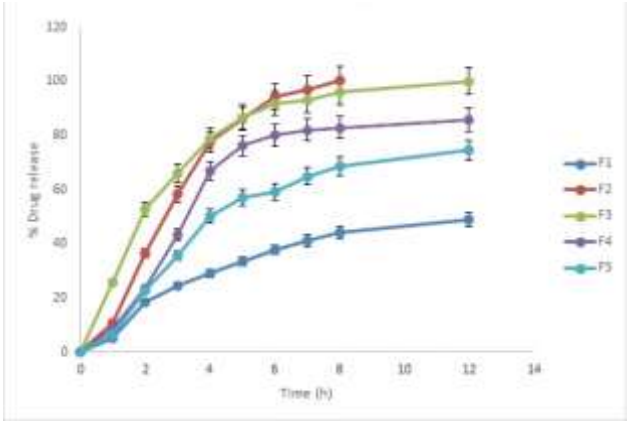

Fig. 4: *In vitro* drug release profile of Neratinib matrix floating tablets (F1-F5)

DISCUSSION

Pre-compression parameters of powder mixture

The tapped and bulk densities results revealed that the packing arrangement in all powder formulations does not significantly change, regardless of the difference in the proportion with respect to the polymers used (Carbopol, MCC & EC). Hausner's ratio (HR) and Carr's index (CI) were found to be excellent, which is to assess the inter-particle friction, potential compression bonds and their stability respectively. The angle of repose was within 21.4±0.29º-27.02±0.08º, this revealed flowability conforming to be okay for compression. All the micromeritics results were with-in the USP limits as showed in the table 2.

Post-compression parameters of tablets

The tablet hardness had minimal effect on drug release profile in a gastro-retentive drug delivery system but was a significant aspect with respect to tablet floating. The floating lag time is increased by increasing the tablet hardness. The friability and content uniformity and weight variation of the tablets were found to be uniform as shown in the table 3.

Drug excipients compatibility studies

The pure neratinib and optimized formulation (F3) FT-IR spectra showed all the normal peaks present as shown in fig. 1. No significant changes in the standard peaks in F3,

which clearly showed no interaction between the polymers and drug used in the matrix floating formulations.

In vitro buoyancy studies

Generally, GET was 4 h in the stomach, the buoyancy formulations extended GRT, therefore increase the absorption of the drug. To achieve *in vitro* floating in the system an effervescent system was adopted. A gas generating agent sodium bicarbonate was added. When the matrix tablet comes in contact with dissolution medium (0.1 N HCl), the evolution of carbon dioxide was trapped and enclosed inside the gel matrix developed by the hydration of carbopol and MCC, hence the density of the tablet decrease less than the medium and thus tablet floating on the surface of the medium. The evolution of CO_2 gas from the matrix floating tablet leaving gas effervesces or pores enhanced the active release drug from the matrix floating tablet. Compared to all formulations, the floating tablet (F1) showed the least floating lag time.

Water uptake study (WU)

All formulations of the floating matrix (F1-F5) showed improved radial and axial swelling. Table 3 shows the % swelling index of F1-F5. The highest percentage of swelling was observed at 12h in F4 (359.23%) as shown in fig. 3 and the lowest percentage swelling F1 (128.66 %). There are considerable differences seen in the swelling property by changing the proportions of carbopol 940, MCC and EC. As the concentration of carbopol 940 and MCC increases, the tablet swelling percent also increases. The drug diffusion could be significantly reliant on the water content of the matrix, because of the mobility of the polymer chains (Saisivam *et al*., 2013). The relaxation of the polymer chain occurs when the water content is high, which could increase the diffusion of the simulated gastric fluid into the matrix tablet, resulting in a speedier generation of CO2 (gas) that decreases the FLT. Therefore, the rate of drug release was found to be reduced initially and then slowly increased. This is due to faster and excessive tablet swelling led to decreases diffusion rates.

In vitro dissolution studies

Based on the review literature, floating systems can prolong the GRT and thus enhance the general drug bioavailability (Qi *et al*., 2015; Mohamed Rahamathulla *et al*., 2013). This floating systems exhibits increase drug absorption at the stomach (upper GIT) instead of the intestine. The various proportions of polymers used showed a significant impact on the *in vitro* drug release. To sustain the release of drug from the prepared formulations (F1-F5) by a combination of both hydrophilic and rate retarding polymers. In all floating matrix tablet formulations, slow diminution of matrix thickness throughout the drug studies is due to polymer erosion. During the experiment, it was observed that the polymer in the matrix rapidly swelled in the dissolution medium at 6-8 h, and then the reduction of the matrix was seen after 12 h, due to an erosion of the matrix polymer, F1 shows the least release of drug 49% at 12 h, this may be due to the presence of rate retarding polymer EC. F2 exhibits at 8 h nearly 100% of drug release (absence of EC). The outcomes results showed that an increase in the concentration of carbopol 940 and MCC without ethyl cellulose increased the drug release. F3 showed sustained release pattern, at the end of 12 h, it exhibits nearly 100 % of drug release (13% carbopol 940 and 10% MCC), and this might be because of the development of dense viscous barrier of the gel on the matrix tablet. If the viscosity of the barrier of the gel increases on the matrix, more time is required to the diffusion of drug. Similarly, the formulations F4 and F5 exhibited 86% and 75% drug release respectively at the end of 12 h, showed a slow profile of drug release. After applying one way ANOVA, the *in vitro* dissolution rate of tablet formulations results were found to be significant ($p<0.05$). However, compared to other matrix formulations, F3 showed significant drug release profile. The *in vitro* release data shows that the drug release from the matrix tablet is directly related to the concentration of both polymers used, i.e. carbopol 940 and MCC. As the concentration of carbopol 940 increase from (7-13%), and MCC (7-10%), the drug release rate was improved. Furthermore, the increased concentration of both the polymers up to 27%, the rate of drug release was retarded. This was due to the formation on the matrix tablet a thick viscous hydrophilic gel that slowed the release of the drug from the formulation, hence this proportion of the polymers could be used for control drug delivery system. The drug release data showed that the carbopol 940 and MCC might be used to prepare sustained floating drug delivery. The formulations F3 exhibited continuous release of drug for up to 12h, hence it was selected as optimized formulation. At present, there is no sustained preparation of anti-cancer drug neratinib in the market. Sustained floating release tablets of neratinib were successfully prepared in the present research work. So, in the near future, we are planning to carry out *in vivo* and pharmacokinetic studies for the optimized formulation and better treatment for cancer in the future.

Mechanism of drug release

In the Korsmeyer - Peppas model the mechanism is not Fickian diffusion or anomalous if the value for n is 0.5 or less, and the value for n >0.45 but less than 0.89 (Peppas *et al*., 1985). The formulations F1, F2, F4, and F5, was found to be non-Fickian release and F3 Fickian release. This model is employed to look at the release of drug from the dosages, if more than one type of mechanism of drug release or not well Known release mechanism. Formulations F1, F3, F4 and F5 were best fitted to Peppas release. However, formulation F2 is not a Fickian with 1st order release.

Table 4: Kinetic studies of Neratinib floating matrix tablets (values of r^2, k and n) and drug release mechanism

F No	Matrix		1st order		Zero order		Hix crow		Korsmeyer-Peppas			Mech. of drug rel.	Release kinetics
	r^2	K	r^2	k	r^2	K	r^2	K	r^2	K	N		
F1	0.9945	14.71	0.9283	9.06	0.8482	5.31	0.905	7.71	0.9950	13.06	0.5671	Non-Fickian	Peppas
F2	0.9513	20.76	0.9946	12.27	0.9567	7.71	0.9893	11.03	0.973	7.04	1.0803	Non-Fickian	1st order
F3	0.9303	18.60	0.8297	14.23	0.8201	13.03	0.9554	7.71	0.9536	20.69	0.3679	Fickian	Peppas
F4	0.9536	30.99	0.8887	10.44	0.8780	9.30	0.9951	8.07	0.9492	13.10	0.9800	Non-Fickian	Peppas
F5	0.9543	22.15	0.9384	11.12	0.8575	8.04	0.9160	10.03	0.9418	10.02	0.9450	Non-Fickian	Peppas

CONCLUSION

In the current study, the sustained release matrix neratinib floating tablets were successfully developed through direct compression technique by combining carbopol and MCC and SB as a gas generating agent. The optimized matrix floating tablets F3, which contain Carbopol 940 (13 %, w/w), and MCC (10 %, w/w) showed satisfactory output in respect of TFT, FLT, the percentage of swelling index and sustain drug release for12 h. Thus, the developed formulation might be used as a promising oral sustained drug delivery of anti-cancer neratinib by floating drug delivery system. Imminently, we are designed to carry out *in vivo* and pharmacokinetic studies for the optimized floating tablet and enhance the bioavailability of neratinib for better treatment for breast cancer.

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