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IN-VITRO AND *IN-VIVO* EVALUATION TESTS FOR FLOATING DRUG DELIVERY SYSTEMS: A REVIEW

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ABSTRACT

The purpose of writing this review on evaluation tests that can be done for floating drug delivery systems (FDDS) was to amass the literature presenting the evaluation tests of various dosage forms that comes under FDDS. With advancements in the technology various dosage forms were designed in such a way that they reside in the stomach for a prolonged period of time releasing the drug at predetermined levels. Evaluation tests are of prime concern in evaluating the success of dosage form. This article gives a glance of all evaluation tests that can be done for various FDDS.

Keywords: *In-vitro tests*, *In-vivo tests*, evaluation tests, floating systems, gastro retentive

INTRODUCTION

Among all the routes of administration, oral route is the most preferred route due to its advantages like patient compliance, ease of administration, flexibility in formulation, comparatively low cost of therapy etc. For the past few decades enormous research is being done in the area of oral controlled drug delivery systems. Of special interest, the dosage forms those retain in gastrointestinal tract for prolonged period and release the drug at controlled rate are also under study. [1, 2] Several approaches are currently utilized in the prolongation of the gastric residence times (GRT), including floating drug delivery systems (FDDS), [3] low- density systems, [4] raft systems incorporating alginate gels, [5] bioadhesive or mucoadhesive systems, [6] high-density systems, [7] superporous hydrogels [8] and magnetic systems. [9] Types of FDDS include non-effervescent and effervescent type covering tablets, [10] capsules, [11] granules, [12] beads, [13] microspheres, [14] superporous hydrogels [15] and in-situ gels. [16]

The present review article is aimed at addressing briefly about the evaluation tests that can be done for FDDS. Evaluation tests for FDDS are presented here as (A) SPECIFIC TESTS and (B) COMMON TESTS.

(A) SPECIFIC EVALUATION TESTS FOR FDDS:

TABLETS & GRANULES
Floating drug delivery systems like floating tablets can be tested for various parameters. In case of tablets, pre-compressed tests and post-compressed tests exist.

Pre-compression tests: The pre-compressed tests under tablets are similar to that of floating granules.

Angle of repose: [17-20] *"It is the maximum angle possible between the surface of a pile of powder and horizontal plain."* It is a pre-compression parameter used for the determination of flow property of

powders/ granules, represented by 'θ'. It can be determined by funnel method [17]. It can be done by taking the accurately weighed powder blend and allowing it to flow freely through the funnel, fixed to a stand at definite height. The height (*h*) and diameter (*d*) of the powder cone are measured and the angle of repose can be calculated by the formula,

$$\tan \theta = {}^h/_r \text{ (or) } \theta = \tan^{-1} {}^h/_r$$

The flow property of powders can be determined by its standard relation with angle of repose which is given in table-1.

Tapped density & Bulk density: [17, 21] Tapped and bulk densities are the pre-compression parameters used in assessing the compactness of the tablet. Loose bulk density (D_b) is the ratio of weight of the untapped powder sample to its initial volume. Tapped bulk density (D_t) is the ratio of weight of the powder sample to its tapped volume. According to ICH guidelines, they can be determined by introducing specific weight of powder blend (W) from each batch in a 100 ml graduated measuring cylinder. Initial volume of the powder (V_b) has to be noted and the measuring cylinder is tapped on a surface, to allow the volume to fall down under its own weight. The measuring cylinder is lifted 50-60 times per minute and carried out for 200 taps, from a height of 2.5 cm. An average has to be taken out of 3 trails. The process has to be again repeated using 400 taps and should be seen that the difference between the 2 volumes obtained after 200 and 400 taps should not exceed 2%. If it exceeds 2 %, then additional tappings were carried out. The Loose bulk density (D_b) and the Tapped bulk density (D_t) can be calculated from the following equations,

Loose Bulk density (D_b) = W/V_b
Tapped Bulk density (D_t) = W/V_t

Carr's Compressibility index and Hausner ratio: [17, 20, 22, 23] These are the pre-compression parameters that are measures of the relative importance of inter-particulate interactions. The Carr's compressibility index (also called as Carr's Consolidation index or Carr's Index) and Hausner's ratio can be calculated from the measured values of tapped density (D_t) and bulk density (D_b), as follows,

Carr's Compressibility index = $(D_t - D_b)/D_t$ x 100

Hausner's ratio = D_t/D_b

Carr's index as an indication of powder flow is given in table-2.

Hausner ratio standard values: < 1.25 = Better flow; > 1.25 = Poor flow

Size & shape: [18, 24, 25] Size and shape can be determined commonly, by using microscope. The particle size and shape plays a major role in determining solubility rate of the drugs and thus potentially its bioavailability. The dimensions of the formulation can be determined by using the suitable method like Vernier calipers, Screw gauge, Sieve analysis, Optical microscope, Air elutriation analysis, Photoanalysis, Electroresistance counting methods (Coulter counter), Sedimentation techniques, Laser diffraction methods, ultrasound attenuation spectroscopy, Air pollution emissions measurements etc.

Tests specific to floating granules as final formulation:
Content uniformity test: [12] In case, if floating granules is the final formulation, then content uniformity test has to be done for granules itself, otherwise it can be done for tablets as mentioned in coming section. Accurately weighed quantity of granules containing certain equivalent weight of drug has to be transferred into a mortar and crushed with pestle to get a powder mass. This mass has to be dissolved in a suitable solvent and stirred if required. Then the mixture has to be filtered and can be analyzed spectrophotometrically as per the λ_{max} of the drug as given in its monograph or as per the specific reference.

In-vitro buoyancy studies: [12]
Fifty unit granules or certain weight of granules are to be placed in 900 ml of distilled water and/or simulated gastric fluid (pH 1.2) in a vessel maintained at 37°C ± 0.2°C and has to be stirred at 50 and 100 rpm in a USP type II (paddle type) dissolution rate test apparatus. The percentage of floating granules for certain period has to be determined, and the floating times are to be measured by visual observation.

Swelling studies: Certain weight of dry granules have to be transferred to a USP dissolution rate test apparatus type-II (paddle type), containing 900 ml of 0.1N HCl (pH – 1.2) as the medium, maintained at a temperature of 37±0.5^0 C throughout the study. After certain intervals, the granules have to be collected carefully from the basket and are re-weighed (W_2) after removing the excess amount of medium, using filter paper. The extent of swelling index can then be measured in terms of weight gain of the granules using the formula,
% Swelling index (W_U) = $(W_2 - W_1)/W_1$ x 100

Post-compression tests:

***Thickness*:** [10, 26, 27] It is the post-compression parameter which is related to dimensional specifications. It can be measured by using calibrated Vernier calipers. In this, an average of three tablets from each formulation can be noted. The tablet thickness should be controlled within a ±5% variation of a standard value.

***Diameter*:** [18] It is the post compression parameter which can be measured by using a calibrated Screw gauge. In this, three tablets from each formulation were taken and the diameter of each tablet has to be noted. Then the average diameter and the standard deviation of each tablet can be determined.

***Hardness test*:** [18, 28] Hardness indicates the resistance of the tablet to withstand the mechanical stress, while handling. The crushing strength (kg/cm^2) of each tablet, selected at random, from each batch can be determined by using various hardness testers that are operated manually: Monsanto Tablet hardness tester, Pfizer hardness tester and Strong Cobb hardness tester. The average hardness and the standard deviation were determined.

***Weight variation test*:** [18, 29] According to weight variation test, 20 tablets, selected randomly from a batch are to be weighed individually and their average weight has to be calculated. The weight of each tablet (w) is then compared with the average weight (w). The tablets are said to meet the weight variation test if not more than 2 tablets out of 20, cross the maximum percentage limits of variation. According to USP & IP, the maximum % variation allowed is given in table-3 & 4 respectively. The % weight variation can be calculated by the formula,

% weight variation = $[(|\bar{w} - w|)/ \bar{w}]$ x 100

***Friability test*:** [17, 18, 30] The friability test for tablets can be done using Roche friabilator. Ten tablets from each batch has to be selected randomly, weighed (W_1) and finally transferred into a friabilator which has to be operated at 25 rpm for 4 minutes i.e. for 100 revolutions. Then the tablets have to be de-dusted by passing through sieve #22 and weighed (W_2). The % friability can then be calculated by using following formula,

% Friability = $(W_1 - W_2)/W_1$ x 100

Each batch has to be analyzed in triplicate, for accurate result. The batch is said to pass the test if the value of % friability of tablets is < 1%.

***Content uniformity test*:** [28, 31] It is the test performed to ensure the proper mixing of tablet contents. Percentage drug content provides information about, how much amount of the drug was present in single formulation. It should not exceed the limits acquired by the standard monographs. Five randomly selected tablets have to be weighed and powdered. The powdered tablet equivalent to 20 mg drug has to be taken and dissolved in suitable solvent and volume made up to 100 ml. Then the drug content has to be analyzed by using the suitable analytical method as specified in the drug monograph.

***In-vitro buoyancy studies / Floating test*:** [11, 17, 32, 33] It is the post compression parameter which is used for the determination of Floating Lag Time/Buoyancy Lag Time (BLT) and Total Floating Time (TFT). The time required for the formulation to float on the surface of simulated gastric fluid from the time of introduction is called Floating Lag time / Buoyancy Lag time (BLT). The total time for which the formulation remains buoyant is called Total Floating Time (TFT). From each formulation, randomly selected tablets are to be immersed into a 900 ml simulated gastric fluid in a USP dissolution test apparatus type-II (paddle type) in which the speed of rotation is maintained at 50 rpm / 100 rpm and temperature maintained at 37 ± 0.5^0 C. Then the BLT and TFT of the formulations can be calculated.

***Swelling studies*:** [10, 28, 33] Swelling index describes the amount of water absorbed by the tablet, thereby increasing the weight and volume of the tablet. These swelling studies can be carried out in USP dissolution rate test apparatus type-II (paddle type), containing 900 ml of 0.1N HCl (pH − 1.2) as the medium, maintained at a temperature of 37 ± 0.5^0 C throughout the study. Weight of individual tablet (W_1) has to be taken initially and is introduced into a basket, for swelling study. After every 1 hour interval, the tablet has to be removed carefully from the basket and is re-weighed (W_2) after removing the excess amount of medium, using filter paper. The extent of swelling index can then be measured in terms of weight gain of the tablet using the formula,

% Swelling index (W_U) = $(W_2 − W_1)/W_1$ x 100

***In-vitro drug release studies*:** [11, 28] These studies can be performed in USP type-2 (paddle type), using 900 ml of simulated gastric fluid, 0.1 N HCl pH 1.2. The temperature has to be maintained at 37 ± 0.5^o C and the rpm maintained with respect to drug in general 50 rpm. The formulation has to be dropped in the dissolution medium once the specified conditions are maintained. 5 ml of sample has to be collected

periodically at regular intervals of time and has to be replaced with a fresh medium, to maintain sink conditions. The collected samples have to be filtered and evaluated spectrophotometrically at a specific λ_{max} of the drug.

CAPSULES

Weight variation test: [34] The procedure is similar to that of tablets but the limits for capsules weight variation permitted are given in table-5:

Content uniformity test: [34] Ten randomly selected capsules have to be collected and the powder has to be separated carefully. Certain weight of powder equivalent to a fixed amount of drug has to be taken, dissolved in a suitable solvent and make up the volume to 100 ml. Then the drug content has to be analyzed by using the suitable analytical method as specified in the drug monograph.

In-vitro buoyancy studies: [11] The capsule has to be immersed in 900 ml of citrate phosphate buffer pH 3 (simulating the pH of the gastric contents in the fed state) or 0.1 N HCl of pH 1.2 (simulating gastric fluid) contained in a USP paddle type apparatus where the speed of rotation maintained at 50 rpm. The amount of time during which the capsule remained buoyant has to be noted as floating time.

NOTE: If the filling mixture of capsule is granular or powder mixture, then the related evaluation tests as mentioned under pre-compression tests of tablets have to be done.

In-vitro drug release studies: [35-37] A filled capsule shell has to be placed in a cylindrical basket, which has to be immersed in 900 ml of dissolution medium 0.1 N HCl of pH 1.2 maintained at 37± 0.5° C. The stirring speed of basket can be maintained at 75 or 100 rpm. Samples of the 5 ml are to be withdrawn at selected time intervals and replaced with an equal volume of drug free dissolution medium. The samples are to be suitably diluted, if required, with blank dissolution fluid and are to be analyzed spectrophotometrically.

The dissolution studies for floating type of capsules can also be carried out in USP dissolution type-II (paddle type) test apparatus containing 900 ml of 0.1 N HCl of pH 1.2 at 50 rpm. The whole system of the dissolution test has to be thermally controlled at 37±0.5° C. An aliquot of 5 ml sample has to be withdrawn at prefixed intervals and the same volume of fresh medium has to be replaced. The samples are to be filtered and analyzed spectrophotometrically.

ALGINATE BEADS

Size and shape: [38-40] The size and shape of beads can be determined by using optical microscopy with stage micrometer or size can be determined by using screw gauge. The mean size can be determined arithmetically.

Determination of percent yield: [41] Percentage yield of microspheres can be estimated by weighing the dried microspheres that were prepared and substituting in the equation,

Percentage yield = (Practical yield / Theoretical yield) x 100.

Determination of drug entrapment efficiency: [41] Certain weight of beads has to be taken, crushed in mortar & pestle and dissolved a in suitable solvent. The mixture has to be stirred for certain duration and after filtering and dilution, the sample can be analyzed spectrophotometrically to determine the entrapment efficiency and loaded drug quantity.

Drug entrapment efficiency = [(Practical amount of drug present in sample)/ (Theoretical amount of drug expected in sample)] x 100

In-vitro buoyancy studies: [38, 41] The time between the introduction of the beads into the medium and its buoyancy to the upper one third of the dissolution vessel (buoyancy lag time) and the time for which the formulation constantly float on the surface of the medium (duration of buoyancy) are to be determined. Percentage of floating can be estimated by the following equation,

Floating percentage = [(weight of beads floating over the medium) / (total weight of beads dropped in the medium)] x 100.

In-vitro drug release studies: [38, 41, 42] In-vitro dissolution studies for beads can be done using USP type-II (paddle) dissolution rate test apparatus. Accurately weighed beads of equivalent drug has to be dropped into 900 ml of HCl buffer (pH 1.2) maintained at a temperature of 37±0.5° C and paddle maintained at a speed of 50 rpm.

At different time intervals, a 5 ml aliquot of the sample has to be withdrawn and the same volume has to be replaced with plain dissolution medium. The collected samples are to be filtered and analyzed with UV Visible spectrophotometer using 0.1 N HCl buffer (pH 1.2) as blank.

Swelling studies: [43] Beads can be studied for swelling characteristics. Sample from drug-loaded beads (only those batches having good drug content and entrapment efficiency more than 50%) has to be taken, weighed and kept in wire basket of USP dissolution apparatus II. The basket containing beads has to be put in a beaker containing 100 ml of 0.1 N HCl (pH 1.2) maintained at 37° C. The beads are to be periodically removed at predetermined intervals and weighed. Then the swelling ratio can be calculated as per the following formula:

Swelling index = [(WWM – WDB) /WdB] x 100

WWB: weight of wet beads
WDB: weight of dry beads
WdB: weight of dried beads

IN-SITU GELLING SYSTEMS

In-situ gelling systems are actually formulated as sol forms and upon administration they undergo in-situ gelation to form a gel. The formation of gel depends upon factors like temperature modulation, pH changes, presence of ions and ultra-violet irradiation, from which drug gets released in sustained and controlled manner. [44-46] The system utilizes polymers that exhibit sol-to-gel phase transition due to change in specific physico-chemical parameters.

Determination of drug content: [47, 48] Certain weight of formulation equivalent to an amount of drug has to be dissolved in a suitable medium, stirred for required time, filtered and analyzed for drug content. It can be done as per the analytical method specified in the monograph of that particular drug used in formulation by following equivalent weight calculation.

pH determination: [45, 46] The pH of solution can be determined using digital pH meter and the favorable conditions that facilitate in situ gelling can be identified. The influence of pH on the gelation of sol can be determined by using the medium of various pH values.

In-vitro gelling capacity: [44, 47, 49, 50] In general the gelling capacity of an in-situ gel forming system can be determined by formulating a colored solution of in-situ gelling system for visual observation. By adding the in-situ gelling formulation to a medium (simulating gastric fluid), various parameters like the time taken for in-situ gel formation, its stiffness and the duration for which the formed gel remains intact, can be estimated.

In-vitro buoyancy studies: [44, 51] After adding a fixed volume of in-situ gelling formulation to a medium (simulating gastric fluid), the parameters like the time taken for the system to float over the surface of medium (floating lag time) and the time the formed gel constantly float over the surface of the dissolution medium (floating time) can be estimated.

In-vitro drug release studies: [52, 53] The release rate of drug from in situ gel can be determined using USP dissolution rate testing apparatus I (basket covered with muslin cloth) at 50 rpm. 900 ml of 0.1 N HCl can be used as dissolution medium and temperature of $37\pm0.5°$ C can be maintained. 5 ml samples can be withdrawn at various time points for estimating the drug release using UV-Visible spectrophotometer. Same volume of fresh medium has to be replaced every time the sample is withdrawn. The drug release studies from in-situ gel can also be done using plastic dialysis cell.

Measurement of rheological property of sol and gel: [53] Viscosity of the sol's prepared using various concentrations of gelling agents can be determined by viscometers like Brookfield viscometer, Cone & plate viscometer etc., Viscosity of the formed gel can also be determined to estimate the gel strength.

Water uptake study: [16, 44, 53] Once the sol is converted to gel, it is collected from the medium and the excess medium was blotted using a tissue paper. The initial weight of thus formed gel has to be noted. Again the gel has to be exposed to the medium/distilled water and the same process is repeated for every 30 min to note down the weights of the gel at each interval after removing the excess amount of medium/distilled water, using filter paper. The weight gain due to water uptake has to be noted from time to time. Effect of pH, concentration of gelling agent/cross linking agent on viscosity, in-situ gelation character, floating ability and drug release can be studied for in-situ gelling type of floating formulations.

HYDROGELS

Scanning electron microscopy: [54-56] Scanning Electron Microscope (SEM) at an operating voltage of 30kV can be used for the study of superporous hydrogel systems (SPH) – A novel approach to extend the gastric residence time. It clearly gives information about the internal porous structures (viz. arrangement of polymers around the pores, formation of capillary channels, interconnected pores etc.,) and morphology of the formulated SPH's.

Determination of density: [54, 57] The bulk density (apparent density) of super porous hydrogels (SPH) or super porous hydrogel composites (SPHC) can be determined following liquid displacement method. A piece of dried hydrogel with known weight has to be immersed in a known volume of hexane in a graduated cylinder. The increase in the volume of hexane can be measured as hydrogel volume. Then, the bulk density of the hydrogel can be calculated by using the equation, Density = Mass/ Volume.

The bulk density of SPH can also be determined by using mercury porosimeter. At low pressure around 0.5 psia where there is no intrusion of mercury takes place into the pores of hydrogel, the rise in volume of mercury on addition of hydrogel has to be noted. That increased level of volume of mercury is the volume of hydrogel whose weight is already known. Hence, bulk density can be determined using the equation, Density = Mass/ Volume.

The true density of SPH can also be determined by using mercury porosimeter. At high pressure around 60,000 psia where there is intrusion of mercury and fills all pores of SPH, the rise in volume of mercury on addition of hydrogel has to be noted as the true volume of the SPH. Hence, true density can be determined using the equation, Density = Mass/ Volume.

Therefore, bulk density, ρ_{bulk} = Mass / Volume$_{0.5\ psia}$

True density, ρ_{true} = Mass / Volume$_{60,000\ psia}$

Determination of porosity: [50, 58] The porosity of super porous hydrogels (SPH) can be determined by following liquid displacement method. The process includes immersion of dried SPH in hexane and keeping it aside overnight. It is weighed after excess hexane on the surface is blotted with filter paper. Then the porosity of SPH can be calculated using the equation,

Porosity = V_p / V_t

Where, V_p = (V_t - V_{SPH}). 'V_p' is the pore volume of SPH; 'V_t' is the total volume of the SPH and 'V_{SPH}' is the true volume of SPH. Total volume of SPH can be measured from its dimensions, as it is cylindrical in shape.

Swelling studies: [57, 58] Hydrogel has to be weighed and added to the respective medium. After every interval either 30 min or 1 hour the hydrogel has to be taken out and blotted with filter paper to remove excess water from the surface. Swelling index can be calculated by using the equation,
Swelling index = [(FW – DW) / DW] x 100.
FW: final weight
DW: dry weight

Water retention: [15, 59] Water retention capacity (WR$_t$) as a function of time can be determined using the equation:

$$WR_t = (W_p - W_d) / (W_s - W_d)$$

where W_d is the weight of the dried hydrogel, W_s is the weight of the fully swollen hydrogel, and W_p is the weight of the hydrogel at various exposure times. For determination of the water-retention capacity of the hydrogels as a function of the time of exposure at 37° C, the water loss of the fully swollen polymer at timed intervals can be determined by gravimetry.

In-vitro buoyancy studies: [60] *In-vitro* buoyancy can be conducted by placing the hydrogel in simulated gastric fluid of pH 1.2 as per USP. The time required for the hydrogel rising to the surface and float can be determined as floating lag time. The time for which the hydrogel remains floating over the surface of the medium can be estimated as buoyant or floating time.

Determination of drug content: [47, 48, 59] Certain weight of formulation equivalent to a fixed amount of drug has to be treated with the medium, mixed well for sufficient time and make up the volume to 100 ml. The mixture has to be filtered and drug content estimation can be done using suitable analytical method as prescribed in its monograph.

In-vitro drug release studies: [58, 59]
The release rate of drug from SPH-DDS can be determined using USP type II (paddle) dissolution rate test apparatus. The dissolution test uses 900 ml simulated gastric fluid, temperature maintained at 37 ± 0.5° C and 50 rpm. 5 ml samples can be withdrawn using a membrane filter at various time points for estimating the drug release using UV-Visible spectrophotometer. Same volume of fresh medium has to be replaced every time the sample is withdrawn.

MICROSPHERES

Surface topography: [61-63] The shape and surface morphology of microspheres can be examined by using Scanning Electron Microscope (SEM) from which the photomicrographs before and after the drug release are to be obtained for study.

Determination of percent yield**:** [62] Percentage yield of microspheres can be estimated by weighing the dried microspheres that were prepared and substituting in the equation,

Percentage yield = (PY / TY) x 100.
PY: Practical yield
TY: Theoretical yield

Determination of entrapment efficiency**:** [62] Equivalent weight of dried microspheres has to be dispersed in a suitable solvent which can extract drug from the microspheres, using magnetic stirrer, for suitable period. Then the mixture has to be filtered and then analyzed spectrophotometrically to evaluate the percent drug entrapped within the microspheres.

Particle size analysis**:** [62] Particle size of prepared microspheres can be measured using an optical microscope with stage micrometer. The mean particle size can be calculated by measuring 100 microspheres.

In-vitro buoyancy studies (buoyancy percentage)**:** [14] Microspheres of certain weight has to be spread over the surface of a USP type II dissolution rate test apparatus containing 900 ml of 0.1N HCl (containing 0.02% tween 80). The medium has to be agitated with a paddle rotating at 100 rpm for 12 hours. The floating and the settled portions of microspheres are to be recovered separately. Both the sections of microspheres are to be dried and weighed. Buoyancy percentage can be calculated as the ratio of the mass of the microspheres that remained floating and the total mass of the microspheres.

In-vitro drug release studies**:** [14, 62] The release rate of drug from microspheres can be determined using USP type I (basket) or type II (paddle) dissolution rate test apparatus. The dissolution test uses 900 ml stimulated gastric fluid, temperature maintained at $37\pm0.5°$ C and 50/ 75/ 100 rpm. 5 ml samples can be withdrawn using a membrane filter at various time points for estimating the drug release using UV-Visible spectrophotometer. Same volume of fresh medium has to be replaced every time the sample is withdrawn.

(B) COMMON EVALUATION TESTS FOR FDDS: These tests are common for all FDDS and applicable to all the FDDS discussed above.

Drug release profiling/Drug release kinetic studies**:** [28, 64-66] To analyze the *in-vitro* drug release, the data obtained has to be fitted to the zero order, first order, Hixon-Crowell model, Higuchi model and

Korsmeyer-Peppas model. For each plot, the regression lines are to be calculated.

a. Zero Order Kinetics**:** It can be represented by the following equation;

$Q_t = Q_0 + k_0 t$

Where, Q_t = amount of drug released in time, t; Q_o = initial amount of drug in the solution; k_0 = zero order release constant.
Graph: % of drug remained to be released *vs.* time.

b. First order kinetics**:**
$\text{Log } Q_t = \text{Log } Q_0 + kt /2.303$
Where, Q_t = amount of drug released in time, t; Q_0 = initial amount of drug in the solution; k = first order release constant.
Graph: logarithmic value of % drug remained to be released *vs.* time.

c. Higuchi model**:**
Simplified Higuchi model can be expressed by following equation:
$f_t = k_H t^{1/2}$
Where, k_H = Higuchi diffusion constant; f_t = fraction of drug dissolved in time, t.
Graph: cumulative % release of the drug *vs.* square root of time.

d. Hixon-Crowell model (or) Cube root equation**:**
$K_t = W_0^{1/3} - W_t^{1/3}$
Graph: The difference between the cube root of initial amount of drug (W_0), to the cube root of amount of drug released at time 't' (W_t) has to be plotted against time.

e. Korsmeyer-Peppas model**:** [67-69]
Korsmeyer developed a simple, semi-empirical model, relating exponentially the drug release to the elapsed time (t). To find out the mechanism of drug release, first 60% drug release data has to be fitted in Korsmeyern-Peppas model

$M_t/M_\infty = kt^n$
Where M_t / M_∞ = fraction of drug released at time, t; k = the rate constant and n = release exponent.
Graph: log cumulative percentage drug release *vs.* log time.
The n value is used to characterize different release mechanisms as given below for cylindrical shaped matrices.
$n \leq 0.45$ indicates Fickian diffusion; $0.45 < n < 0.89$ indicates anomalous (non-Fickian) diffusion; $n = 0.89$ indicates case II (relaxational) transport and $n > 0.89$ indicates super case II transport mechanism.

Anomolous diffusion or non-Fickian diffusion refers to both diffusion and erosion controlled drug release. Case-II or Super case-II transport refers to the erosion of the polymeric chain.

Interpretation:
For each plot, correlation co-efficient, r value (r^2 = coefficient of determination) has to be determined and based on the highest value of r, the release kinetics (zero order or first order) and the release mechanism (diffusion or erosion) can be identified. Higher the 'r' value, better the fit of data to that kinetic model.

Similarity factor (f2): [70-73] It is a model independent approach in which the dissolution profiles of the prepared formulations are compared with marketed preparation (standard). This similarity factor (f2) can be calculated by the equation,
$f2 = 50 \log \{[1 + \frac{1}{n}\sum_{t=1} (R_t - T_t)^2]^{-0.5} \times 100\}$
Where, n = number of sampling time points; R_t = dissolution of reference at time't'; T_t = dissolution of test sample at time't'.
If the value of f_2 lies between 50 and 100, the two dissolution profiles are said to be similar.

Dissimilarity factor (f1): [70-72] The dissimilarity factor (f1) calculates the percent difference between the two curves at each time point and is a measurement of the relative error between the two curves:
$f1 = \{[\sum_{t=1}^{n}R_t - Tt] / [\sum_{t=1}^{n} R_t]\} \times 100$
Where, n = the number of time points; R_t = the dissolution value of the marketed formulation at time, t; T_t = the dissolution value of the test formulation at time, t.
The values should lie between 0-15 in order to confirm that the two products as following similar dissolution profiles.

Statistical analysis: [14] Experimental results can be expressed as mean $\pm$ standard deviation. Student's *t*-test and one-way analysis of variance (ANOVA) can be applied to check significant differences in drug release from different formulations or to estimate the difference between best formulation and marketed formulation. Differences are considered to be statistically significant at $p < 0.05$.

Drug-polymer interactions: [10, 12, 31, 61, 63, 74] The drug-polymer interactions can be studied by Fourier Transform Infrared Spectroscopy (FTIR), Differential Scanning Calorimetry (DSC), Scanning Electron Microscopy (SEM), X-Ray Diffraction (XRD), Hot Stage Polarizing Microscopy (HSPM). These studies are performed to identify any significant changes in the behavior and physical state of the drug and polymer, after mixing.

Stability studies: [28, 33, 58, 75] As per ICH and WHO guidelines, stability studies are performed to assess the stability of the drug and the formulation. It can be performed by taking the formulation in a HDPE (High Density Polyethylene) bottles/ air tight containers and subjecting them to stability study in a stability chamber at 40 ± 2^0 C and $75\pm5\%$ RH for 3 months to 9 months period as per requirement. At specific intervals the samples are to be taken and the samples are to be evaluated for any color changes, hardness, friability, percent drug content, buoyancy, in-vitro drug release etc.

In-vivo studies: [12, 76-82] Once all the above in-vitro tests were performed successfully and a best formulation was identified, the next step is to study the in-vivo behavior of drug release and in-vivo buoyancy studies for that best formulation. In-vivo studies for FDDS are of special case as the buoyancy nature has to be predicted in addition to the drug release profiling.

As per the established in-vivo methods so-far, the in-vivo studies for FDDS can be done in human beings [76, 78, 79] or suitable animal like dog [77], albino rabbits [80, 81] or albino rats [82]. The type of dosage form and the nature of drug are the factors that help in selecting the model i.e. either human model or animal model, for in-vivo studies. The protocol for study has to be approved by the Institutional Ethical Committee and in-vivo procedure has to be done as per that protocol.

a. In-vivo buoyancy studies: For in-vivo buoyancy observation, either radiographic (x-ray) studies or γ-scintigraphy studies can be performed. In case of radiographic studies, $BaSO_4$ can be used as radio opaque material in the formulation whereas in case of γ-scintigraphy, radio-labeled Technetium (99mTc) can be used. After administration of the placebo or formulation, the buoyancy character of the formulation can be noted by the images taken via X-ray or γ-scintigraphy studies at various time intervals.

b. In-vivo drug release studies: In-vivo drug release studies can be done following statistical models like two-way cross over design. Blood samples are to be collected at the predetermined time intervals as per the protocol and the drug analyzed with suitable analytical technique like HPLC after required processing. The data thus obtained can be fitted to various kinetic models and the drug absorption profile can be reported. In addition, various

pharmacokinetic parameters like C_{max}, t_{max}, K_E, $t_{1/2}$, $AUC_{etc.}$ can be determined.

CONCLUSION
Floating drug delivery systems (FDDS) are giving promising results in case of specific drugs having drug absorption window in the upper GIT, particularly in stomach and for those drugs showing problems with alkaline environment. Hence the research in this area is tremendously increasing. Hope the technology will give solution to many such problems with well established evaluation tests.

Table-1: Type of flow as per angle of repose

Angle of Repose	Powder flow
<25	Excellent
25 – 30	Good
30 – 40	Passable*
>40	Very-poor

*May be improved by a glidant, e.g. 0.2% Aerosil

Table-2: Type of flow as per Carr's consolidation index

Carr's Compressibility index (%)	Type of Flow
5-15	Excellent
12-16	Good
18-21	Fair to passable*
23-35	Poor*
33-38	Very poor
>40	Extremely poor

*May be improved by glidant, e.g. 0.2% Aerosil

Table-3: Weight variation test limits for tablets as per USP

Average weight of tablet (mg)	Maximum % variation allowed
<130	± 10.0
130 to 324	± 7.5
>324	± 5.0

Table-4: Weight variation test limits for tablets as per IP

Average weight of tablet (mg)	Maximum % variation allowed
<80	± 10.0
80 to 250	± 7.5
>250	± 5.0

Table-5: Weight variation test limits for capsules as per IP

Average weight of capsule (mg)	Maximum % variation allowed
< 300	± 10.0
> 300	± 7.5

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