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Formulation and evaluation of floating tablet of nimesulide by direct compression method

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Abstract

Nimesulide has been used versatile on fever, pain, inflammation, rheumatoid arthritis, tendinitis, thrombophlebitis and trauma. Common drawbacks of conventional tablet dosage forms of nimesulide show an irritant effect on the stomach due to its weakly acidic nature along it has short duration of action leading to poor bioavailability. A Floating drug delivery system for Nimesulide leads to overcoming the problem related to an irritant on the stomach by avoiding direct contact with the mucosa. Thus, this study was designed and performed to formulate and evaluate the floating tablet of Nimesulide and determine the release pattern of the prepared formulation. Tablets were prepared by direct compression method using different polymers (HPMC, carbopol, and guar gum), either in an individual or in combination. The formulation blend was subjected to various pre-formulation and post-formulation studies including floating lag time, total floating time, hardness, friability, drug content, weight uniformity, and in-vitro dissolution. According to pre- pre-formulation study, the flow property was found to be good to passable. Similarly, all post-compression parameters of floating tablets were found to be within acceptable limits except the friability test of F1 and F2 formulations. The tablet's floating lag time was determined to be in the range of 7-153.5 seconds, and the total floating time was in the range of 4-7 hrs. From the data of dissolution, carbopol showed a slower release of drugs than that of HPMC and guar gum. The use of carbopol as a floating polymer showed release of drugs from dosage form was 84.46% in 7 hrs and 99.10% in 3 hrs with the use of HPMC, 96.39% in 4 hrs with the use of guar gum. A combination of HPMC and guar gum released drugs in a slow release of drugs only for 3 hrs i.e. 98.02% in 3 hrs, the combination of carbopol and HPMC slowly released drugs for 6 hrs i.e. 90.43% in 6 hrs, and the combination of carbopol and guar gum showed maximum slow release of drugs for greater than 7 hrs i.e.74.16% in 7hrs. Hence, among all the formulations, F7 with the combination of carbopol and guar gum as polymer showed a maximum slowed release effect for greater than 7 hrs, which can be taken as the best batch.

Keywords: Nimesulide; Carbopol; HPMC; Guar gum; Floating tablets

1. Introduction

Drug delivery system is an engineered system that carries pharmaceutical compounds throughout the body to release its therapeutic dose in a controlled manner [1]. There has always been higher interest in oral controlled-release drug delivery in the pharmaceutical field to improve therapeutic advantages such as ease of dosing administration, patient compliance, and flexibility in formulation [2]. Those drugs that have short half-lives and can easily be absorbed from the gastrointestinal tract (GIT) are eliminated quickly from systemic circulation. So, such drugs need frequent dosing that leads to fluctuation in plasma drug concentration. To avoid such limitations, oral sustained controlled release

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formulation plays an important role that releases the drugs slowly into GIT and maintains effective plasma drug concentration for a therapeutic period [3]. Gastro-retentive drug delivery systems such as floating tablets retain in the stomach for a prolonged time, release their active ingredients and thereby enable sustained and prolonged input of the drug to the upper part of the gastrointestinal tract [4]. Effective oral drug delivery may depend upon factors such as physiological limitations (variable gastric emptying process, non-uniform absorption profiles, site of absorption of drugs) and pharmaceutical limitations (varying in gastrointestinal transit time of dosage form, incomplete drug release from the dosage form, and shorter residence time of dosage form in the stomach). This leads to incomplete absorption of drugs, whose absorption site is in the stomach and upper part of the small intestine as drugs are passed down from the absorption site before absorption. This ultimately results in the excretion of drugs without complete absorption and hence leads to therapeutic failure. [5] Hence to avoid such problems, a floating drug delivery system is formulated.

A floating drugs delivery system (FDDS) is also called a hydrodynamically based system (HBS), is defined as a system that floats on a gastric content and releases drugs slowly at the desired rate from the system in a stomach. After the release of drugs, the remaining system is passed down from the stomach for elimination. This results in an increased gastric retention time (GRT) that improves bioavailability and controls fluctuation in plasma drug concentration. [6] For a drug with Drugs that are locally active in the stomach and that have a narrow absorption window in the gastrointestinal tract, a floating tablet retains dosage form at the site of absorption and enhances bioavailability [7,8]. The increased bioavailability not only reduces the dosing frequency but also increases therapeutic efficacy and patient compliance. For drugs that are unstable in an intestinal or colonic environment, floating drug delivery is a suitable technique. A floating system retains dosage form in a stomach for a prolonged period resulting in the dissolution of drugs in gastric fluid. This system is suitable for a pathological condition like diarrhea, as it keeps the drugs in the floating condition in a stomach to have a relatively better response of drugs [9]. This system requires the presence of food to delay gastric emptying time and is not suitable for drugs that are unstable in acidic pH and those that irritate GI mucosa [10].

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a class of drugs approved for use as antipyretic, anti-inflammatory, and analgesic agents. It is used to treat pain, fever, and other inflammatory conditions. Due to such pharmacological effects, NSAIDS is useful for treating dysmenorrhea, fever, gout, muscle pain, arthritic conditions, and migraine. Similarly, it is used as an opioid-sparing agent in certain acute trauma cases [11, 12]. Nimesulide is a NSAID with good anti-inflammatory, analgesic and antipyretic activities. It has shown superior antipyretic potency to indomethacin, ibuprofen, aspirin, and paracetamol (acetaminophen) in rats with yeast-induced fever [13]. Also, nimesulide is a relatively weak inhibitor of prostaglandin synthesis in vitro and appears to exert its effects through a variety of mechanisms including free-radical scavenging, effects on histamine release, the neutrophil myeloperoxidase pathway, bradykinin activity, tumor necrosis factor-α release, cartilage degradation, metalloprotease synthesis, phosphodiesterase type IV inhibition, platelet aggregation and synthesis of platelet-activating factor. Animal studies have suggested that Nimesulide is less ulcerogenic than aspirin, indomethacin, naproxen, piroxicam, and ibuprofen [14].

Nimesulide has been used versatile on fever, pain, inflammation, rheumatoid arthritis, tendinitis, thrombophlebitis and trauma. Common drawbacks of conventional tablet dosage forms of nimesulide show an irritant effect on the stomach due to its weakly acidic nature along it has short duration of action. Hence, this results in poor bioavailability of drugs [15]. Similarly, nimesulide is easily absorbed from GIT has a short half-life of 1.3-4.8 hours, and requires multiple doing to maintain the therapeutic effect leading to peak and trough in drug level throughout the therapeutic period [14]. It is also reported that when drugs are administered in the presence of food, the plasma drug concentration increases 2-4 fold than under fasting conditions. Hence in the case of the conventional dosage form, when administered after the meal at bedtime by an arthritic patient, it results in a peak effect in the night itself with practically no effect the next morning. Further, it requires the necessity of another dose the next morning to reduce morning stiffness. Hence conventional dosage form has poor patient compliance [16]. A Floating tablet of Nimesulide leads to overcoming the problem related to an irritant on the stomach by avoiding direct contact with the mucosa. Similarly, it overcomes the problem related to a short half-life as it increases the duration of action of drugs by increasing the retention time of dosage form in gastric PH. These will release drugs into GIT and maintain a constant plasma drug concentration for a longer period and hence decrease the dosing frequency of drugs. Thus, this study was designed and performed to formulate and evaluate the floating tablet of Nimesulide and determine the release pattern of the prepared formulation.

2. Material and methods

2.1. Materials

Nimesulide pure drug was gifted from Aarati Drugs Limited (NMS/10100914). Carbopol, HPMC, Guar gum, sodium bicarbonate, magnesium stearate, talc, lactose and potassium chloride were purchased from HiMedia Laboratories Pvt.

Ltd. Citric acid, boric acid, sodium hydrogen pellets were purchased from Thermo Fisher Scientific India Pvt. Ltd. All reagents and chemicals used were of analytical grade.

2.2. Methods

2.2.1. Formulation design

Table 1 Formulation design

Ingredients (mg)	**F_1**	**F_2**	**F_3**	**F_4**	**F_5**	**F_6**	**F_7**
Nimesulide	100	100	100	100	100	100	100
Carbopol	135	-	-	-	65	100	65
HPMC	-	135	-	65	70	-	-
Guar gum	-	-	135	70	-	100	70
Citric acid	15	15	15	15	15	20	15
Sodium bicarbonate	50	50	50	50	50	60	50
Sodium carboxymethyl cellulose	20	20	20	20	20	20	20
Magnesium stearate	6	6	6	6	6	6.75	6
Talc	6	6	6	6	6	6.75	6
Lactose	28	28	28	28	28	36.5	28
Total weight	360	360	360	360	360	450	360

2.3. Study methods

2.3.1. Preformulation Studies

Physical properties of the drug

Physiochemical properties viz colour, odor, state and solubility of the pure drug were studied followed by the determination of its melting point. The melting point of a substance is the temperature range over which the first crystal of a solid starts to melt and the last crystal completes its melting. this was determined by the Melting point apparatus [17].

Determination of λ_{max}

A standard solution of Nimesulide 10ppm (10µg/ml) in alkaline borate buffer of pH 8.4 was scanned in the UV range of 220-400 nm using alkaline borate buffer as blank [18].

Preparation of standard calibration curve for Nimesulide at 397 nm.

Accurately weighed 10mg Nimesulide was dissolved in 10 ml alkaline borate buffer and further diluted to get a stock solution of 100 µg/ml. This solution was diluted further to give standard concentrations of 2,5,10,15 and 20 µg/ml. The absorbance of these solutions was measured at 390 nm using a spectrophotometer [19].

2.3.2. Precompression Studies

Bulk density (D_b):

It is a ratio of the mass of powder to bulk volume. It is expressed in g/ml. accurately weighed quantity of powder was carefully poured into a graduated measuring cylinder through the large funnel and initial bulk volume was measured [20].

$$D_b = \frac{M}{V_o}$$

Where
M is the mass of powder
V_o is the volume of the powder.

Tapped density (D_t):

It is the ratio of the mass of powder to tapped density. Ten grams of powder was introduced into a clean, dry 100 ml measuring cylinder. The cylinder was then tapped 100 times from a constant height and the tapped volume was read. It is expressed in g/ml and is given by:

$$D_t = \frac{M}{Vt}$$

Where,
M = Mass of powder
V_t = Tapped volume of powder

Angle of repose (**θ**):

It is defined as the maximum angle possible between the surface of the pile of powder and the horizontal plane.

A fixed funnel method was used. A funnel was fixed with its tip at a given height 'h', above a flat horizontal surface to which graph paper was placed. The powder was carefully poured through a funnel till the apex of the conical pile just touched the tip of the funnel [21]. Then, the angle of repose was calculated using the following equation,

$$\theta = Tan^{-1}\frac{h}{r}$$

Where,
θ = Angle of repose
h = Height of pile
r = Radius of the base of the pile

Carr's index:

It is an indication of the compressibility of a powder. It is expressed in percentage and is given by [21]

$$I = \frac{Dt - Db}{Dt} * 100$$

Where,
D_b = Bulk density
D_t = Tapped density

Hausner's ratio:

It is the ratio of the tapped density to the untapped density [22].

$$H = \frac{Dt}{Db}$$

2.4. Preparation of Tablets

All ingredients (nimesulide, HPMC/ carbopol/ guar gum or two combinations, citric acid, sodium bicarbonate, sodium carboxy methyl cellulose, lactose) were accurately weighed and mixed in mortar and pestle for 15 min. Then all of them were passed through sieve number 60. Before compression, accurately weighed magnesium stearate and talc were mixed, and hence mixed powder was compressed in a tablet compression machine. The ingredients used were according to the formulation table 1. [22]

2.4.1. Evaluation of tablets

Weight variation test

A total of 20 tablets were selected randomly and weighed individually and the average weight was determined and compared with the average weight. The tablets should be within the specified limits i.e. ±7.5% of average weight as per USP [21].

Hardness test

It was determined by using a Monsanto hardness tester. Ten tablets were selected randomly and hardness was determined in kg/cm^3 and the average hardness of tablets was calculated. A tablet hardness of about 4-5 kg/cm^3 is considered adequate for mechanical stability [22].

Friability test

20 tablets were selected randomly and the initial weight was taken and kept in a Roche friability tester and was revolved at 20 rpm for 4 minutes. The tablets were taken out, dedusted, and reweighed. The friability of the tablets was calculated as:

$$\text{Percentage friability} = \frac{\text{initial weight} - \text{final weight}}{\text{initial weight}} * 100$$

The weight loss should not be more than 1% as per USP [21].

Thickness test

The thickness of the tablets is a critical criterion for their therapeutic effectiveness. All the tablets, where the API comprises a major part of the tablet are required to meet a weight variation test. The thickness of tablets is determined using Vernier Caliper [23].

Drug content uniformity

20 tablets were weighed and powdered. An amount equivalent to 100 mg of Nimesulide was dissolved in 40 ml of methanol for 20 minutes and its volume was made up to 100 ml of pH 8.4 alkaline borate buffer, which was mixed for 10 minutes, then filtered, diluted appropriately, and analyzed for drug content at 366 nm using UV-Visible Spectrophotometer using the equation of calibration curve [24].

Buoyancy studies

Floating lag time is the time required for the tablet to rise to the surface of the medium. The duration of time at which the dosage form constantly remains on the surface of the medium is called total floating time. This was determined by placing the tablet in 900ml of a plastic container filled with 500ml of 0.1N HCl. This was determined by visual observation. [25]

In-vitro dissolution studies:

The release rate of Nimesulide from the tablets was determined using USP dissolution testing apparatus II (Paddle method). The dissolution test was performed using 900ml of pH 8.4 alkaline borate buffer as a dissolution medium at 37 ± 0.5°C at 100 rpm of paddle speed. A sample (10ml) of the solution was withdrawn at 1-8hrs. The sample was filtered and absorbance of the solution was measured at 366 nm using a UV-visible spectrophotometer and % drug release was calculated using the equation of the calibration curve [23].

3. Results and discussion

3.1. Preformulation studies

Nimesulide pure sample was crystalline powder found to be odorless and yellowish green in color. The melting point was determined to be 143.34±0.577 °C. Nimesulide was found to be insoluble in water, and freely soluble in acetone, methanol, anhydrous ethanol, and borate buffer. The λ_{max} of Nimesulide was found to be 397 nm. The absorbance of the solution from 0 to 25µg/ml was measured in a UV-Spectrophotometer at 397 nm. The linear correlation was found to be R^2=0.9934 with a positive correlation between the variables.

3.1.1. Pre-compression parameters for the powder blend

Pre-compression evaluations were done to ensure the flow properties of the powder blend.

Table 2 Results of Pre-Compression Evaluation Parameters

Formulation Code	Bulk density (gm/ml) Mean± SD	Tapped density(gm/ml)Mean± SD	Angle of repose(□) Mean± SD	Carr's index (%)	Hausner's ratio Mean
F_1	0.57±0.017	0.65±0.005	32.27±0.47	12.75	1.14
F_2	0.55±0.03	0.67±0.005	30.22±0.41	18.71	1.23
F_3	0.50±0.011	0.66±0.005	31.80±0.52	23.61	1.30
F_4	0.56±0.017	0.63±0.005	32.293±0.45	12.041	1.13
F_5	0.58±0.037	0.73±0.005	33.11±0.50	20.22	1.25
F_6	0.57±0.017	0.76±0.005	30.22±0.41	25.65	1.34
F_7	0.54±0.017	0.65±0.005	31.04±1.01	17.34	1.20

The bulk density was determined to estimate the free-flowing property of the powder mixture. The bulk density of all formulations ranges from 0.50-0.58 gm/ml. The tapped density of all formulations was determined to analyze the powder blends for their free-flowing property. The tapped density of all formulations ranges from 0.63-0.73 gm/ml. The angle of repose was used for the measurement of frictional force in a loose powder which in turn will influence the flow properties of the powder blend. The angle of repose ranged from 30.220-33.110 which showed the passable of the powder blend. The compressibility index was the simplest method to measure the free flow of the powder blends of all formulations. The ease with which material was induced to flow was given by the compressibility index of F1, F4 and F7 were 12.75%, 12.04%, and 17.34% respectively, which indicates good flowability while F2 and F5 were 18.71% and 20.22 % respectively, which indicates fair to passable properties while F3 and F6 were 23.61% and 25.65% respectively which indicates poor flow properties as given in Table 2. Hausner's ratio was determined to assess the flow property of the powder blend. Hausner's ratio of powder blend of F1 and F4 are 1.14 and 1.13 respectively which indicates good flow and that of F2, F5 and F7 are 1.23, 1.25, and 1.20 respectively which indicates fair flow. Similarly, F3 and F6 are 1.30 and 1.34 respectively which indicates passable. It was evident from the results of the pre-compression studies that the powder blends of all 7 formulations possess good to passable flow properties, which were within the standard limits and were qualified for compression into tablets.

3.2. Evaluation of tablets

The tablets obtained after compression were evaluated on various parameters to determine their quality and to ensure that the resultant product met all necessary criteria required for the floating tablets.

Table 3 Results of Post-Compression Evaluation Parameters

Formulation code	Weight variation (n=20) (mg) mean±SD	Hardness test (kg/cm^3) (n=3) mean±SD	Friability (%)	Thickness (cm) (n=3) mean±S D	Drugs content (%)	Buoyancy lag time (sec)	Total floating time (hrs)
F_1	0.3607±0.01320	4.16±0.208	1.08	5.0033±0.001528	105.90	153.5	>6
F_2	0.361±0.0105	4.46±0.057	1.85	5.0043±0.002517	104.96	34	>3
F_3	0.350±0.011	4.63±0.152	0.74	5.002±0.001	108.91	35	>3
F_4	0.375±0.065	5.33±0.25	0.56	5.0016±0.0005	107.10	18	>3
F_5	0.352±0.0106	5.5±0.05	0.31	5.0023±0.0005	98.67	7	>5
F_6	0.4366±0.011	5±0	0.18	6.003±0.0015	100.48	124	>7
F_7	0.354±0.013	4.66±0.76	0.04	5.002±0.001	111.32	9.5	>7

3.2.1. Weight variation test

The weight variation test was carried out to ensure that the tablets of each formulation were of uniform weight, which in turn would indicate the uniform distribution of the contents of the powder blends of each formulation. The weight variation for tablets of all formulations was found to be within the US pharmacopeia limits of ±5% as indicated in Table 3. The result indicates that all tablets of each formulation were uniform in weight and passed the test as per the US Pharmacopoeia range.

3.2.2. Hardness test

The hardness of tablets was carried out to determine their resistance to abrasion or breakage during transportation, storage, and handling before usage. Similarly, it determines the floating lag time of a dosage form. The hardness for tablets of all the formulations was found in the range of 4 to 5.5 kg/cm3 as given in Table 3. The results indicate that the tablets of all formulations have good hardness, which in turn protects them from mechanical damage.

3.2.3. Friability test

The friability test was carried out to ensure the mechanical strength of tablets to avoid the loss of the external surface of the tablets during the process of packing, handling, transit, and storage. Friability below 1% was an indication of good mechanical resistance. The results indicate that the friability for tablets of all formulations except F1 and F2 was below 1% and hence passed the test. The results are summarized in Table 3.

3.2.4. Thickness test

The thickness of all formulations was in the range of 5.0016-6.003 cm as shown in Table 3. As the tablet thickness of each formulation was comparable. So, it could be predicted to be a consistent powder blend.

3.2.5. Drugs content (assay)

Drug assay is an investigational procedure to determine the qualitative and quantitative presence of active ingredients. This was determined using UV-visible spectrophotometry by measuring absorbance at 397 nm. The drug content of the formulation was from a range of 98-112% which was summarized in Table 3, which indicates that the percentage release is between 85-115% according to USP.

3.2.6. Buoyancy studies

It includes both the floating lag time study and the total floating time of a floating dosage form. The floating lag time was found to be in the range of 7-153.5 seconds. Among them, F2, F3, F4, F5, and F7 showed a floating lag time of less than 60 sec while F1 and F6 showed a floating lag time of 153.5 sec and 124 sec respectively, which is summarized in Table 3. In the same way, the total floating time was found to be in the range of 3-7 hrs.

3.2.7. In-vitro dissolution test

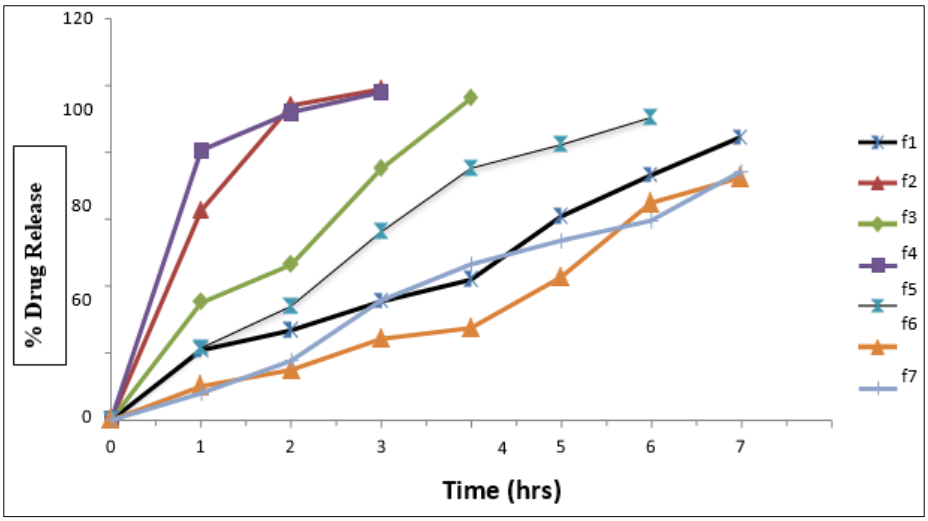

Figure 1 Comparative Drug release profile of prepared formulation

The dissolution study was carried out to evaluate the release profile of the drug with the function of time. It was found that the drugs release and sustain release effects of drugs from dosage form depended on polymer composition and concentration. The dissolution test showed that carbopol showed a sustained release effect from dosage form than that of HPMC and guar gum. Use of carbopol as a floating polymer showed release of drugs from dosage form was 84.46% in 7 hrs and 99.10% in 3hrs (use of HPMC as a floating polymer), 96.39% in 4 hrs (use of Guar gum as a floating polymer). Thus, the use of HPMC and guar gum as floating polymers does not show an effect of sustained release in a dosage form. Similarly, a combination of HPMC and guar gum released drugs in a sustained manner only for 3 hrs i.e. 98.02% in 3 hrs, a combination of carbopol and HPMC released drugs as sustained manner for 6 hrs i.e. 90.43% in 6 hrs, the combination of carbopol and guar gum showed maximum sustained release effect for greater than 7 hrs i.e. 74.16% in 7 hrs as indicated in Figure 1.

Our result showed that HPMC and guar gum showed an initial immediate release of drugs from dosage form than Carbopol from the dissolution study, which was also reported in research of Patel A. *et al.* [26]. This study postulates that the sustained drug release could be ascribed to the polymer carbopol, as it was also reported in the previous work that when carbopol used as a floating polymer resulted in reduced dosage frequency and increased patient compliance with sustained release of Esomeprazole and Clarithromycin- Israr *et al*. [27]. In our study, the use of HPMC resulted in an immediate release of drugs without any control of drug release. However, it showed quiet control in drug release when used in combination with another polymer, which was also observed in research by Eswaraiah *et al.* that HPMC due to its lower viscosity and low molecular weight, could not maintain matrix integrity sufficiently when used alone and did require combination of other polymer to control drug release [28]. The data of dissolution revealed that the combination use of the polymer showed an increase in total floating time than used in individual form. This might be due to an increase in the gelling strength of the polymer, which prevents the escape of involved CO_2 from the polymer matrices leading to a decrease in density of the dosage form. Similarly, the release of drugs was decreased with the use of an amount or combination polymer because the amount of drug bound in the polymer could be more which complies with the study of Davoudi *et al*. [25].

4. Conclusion

The study concluded that Nimesulide can be successfully formulated as an oral floating tablet using various ingredients in different concentrations and different compositions either alone or in combination form by the direct compression method. Similarly, the study concluded that a combination of carbopol and guar gum (F7) gives the best result in the preparation of floating tablets by increasing the floating lag time providing a sustained drug release pattern. Moreover, all the other studied parameters were found to be satisfactory and all the results were as per pharmacopoeial standards. The floating tablet dosage form is a promising future for sustained-release drug delivery for drugs with locally active in the stomach and that have a narrow absorption window in the gastrointestinal tract. Also, this drug delivery system provides an important advantage for drugs that are unstable in an intestinal or colonic environment. Real-time and accelerated stability studies can be carried out along with compatibility studies to optimize the final product.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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