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Original Article

FORMULATION OF POLYMER-NANO COMPOSITE FILM FOR COATING GRASTRORETENTIVE TABLET OF DIPYRIDAMOL AS A MODEL

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ABSTRACT

Objective: The aim of this work was to formulate the polymer nano composite film to coat the gastroretentive tablet.

Methods: The polymer nano composite film was formulated by varying the concentration of Eudragit® RS/RL 30D, PEG 6000 and with or without sodium bentonite. The polymer nano composite was then used to coat the gastroretentive dipyridamol tablet as a model.

Results: The film containing Eudragit® RS/RL 30D at ratio 80:20 with 20 % PEG 6000 (w/w dry polymer) and 2% sodium bentonite (w/w dry clay) (formulation 16) was more elastic and strength. The diffusion test showed that the percentage of dipyridamole passed through the film of formulation 8 (without sodium bentonite) and 16 was superimposed during the 7 first hours and after 7 hours, they split in which the formulation 8 was higher than formulation 16. The floating lag time and capacity of the coated tablet with nano composite were 1': 53" and more than 8 hours, respectively, while for tablet coated without nano composite were 0': 09" and 7': 08': 27" respectively. The release showed that the gastroretentive dipyridamol tablet coated by polymer nano composite (formulation 16) released dipyridamol 43.59±3.59 and 89.69±4.92% at 4th and 8th hour respectively, while the tablet coated without nano composite (formulation 8) released 44.76±4. 74% and 95.76±1.35% respectively.

Conclusions: The polymer nano composite film containing Eudragit® RS/RL 30D with the ratio of 80:20 and 20% PEG 6000 (w/w dry polymer) with the presence of 2% sodium bentonite generated tablet that floated for 8 hours and produced the release of the drug according to the requirement that has been set.

Keywords: Gastroretentive tablet, Floating, Coating, Polymeric nano composite, Dipyridamol, Eudragit® RS/RL 30D, Sodium bentonite.

INTRODUCTION

Dipyridamole is an inhibitor thrombus formation when is given chronically and can cause vasodilatation when is given at a high dose over the short a period of time. The administration of dipyridamole through oral route give a low bioavailability, which was around 37-66%. This is due to the limited absorption site of the compound. The alpha-half-life of dipyridamole was around 40 minutes. It has to be given 4 times daily which will cause uneasiness in patients [1, 2].

Dipyridamole is readily soluble only in an acidic medium, and therefore it can only go into solution from solid pharmaceutical form and then be absorbed if the pharmaceutical preparation remains in the acidic range for a sufficiently long period. So, the solubility and the absorption greatly depend upon the retention time and the pH value in the stomach and the upper intestine [1]. By controlling the release, it is possible to improve the therapeutic effect and bioavailability. Hence it would be beneficial to develop *Control release Gastroretentive dosage form (CR-GRDF)* which can remain in the gastric region for several hours, which would significantly prolong the gastric residence time of this compound and improve the bioavailability, reduce drug waste and enhance the solubility of this drug [3].

Controlled gastric retention of solid dosage form may be achieved by the mechanisms of *floatation, mucoadhesion, sedimentation and expansion or modified shaped system* [4, 5, 6]. Mechanism of mucoadhesion type solid dosage for being where the tablet is prepared as bio adhesion to stomach mucus occurs [7]. Sedimentation mechanism of control gastric retention of solid dosage form is prepared with a high density of dosage form that is retained in the bottom of the stomach [8].

Expansion or modified shaped system is an approach where the dosage form is expanded by swelling or unfolding to a large size which limits emptying of the dosage form through pyloric sphincter [9].

Among all the approaches, the floating drug delivery system is considered as the most effective method. The floating drug delivery system is achieved by alow density form of the dosage form that causes buoyancy in gastric fluid. Low density can be approached by adding low density fillers. The effervescent floating tablet is prepared with the help of sodium bicarbonate and citric acid, while non-effervescent tablet use a gel forming or swellable cellulose type of hydrocolloids and matrix forming polymers [10, 11]. The use these systems only, the tablets will be easily eroded and therefore the tablet is usually coated with proper polymers to mantain its intact. Coating the tablet with polymers will form a rigid tablet which will control the release of the active substance which depends on the permeability of the film. Besides that, the film acts as a barrier, as when the gas from the effervescent system is liberated, it will trap the gas under the film and this will give the buoyancy effect of the tablet. So, the proper film characteristics are good permeability and elasticity.

Eudragit® RL and RS are poly (ethyl acrylate-co-methyl methacrylate-co-trimethylammonioethyl and methacrylatechloride) in a ratio of 1:2:0.1 and 1:2:0.2 respectively. They are insoluble and pH independent swelling, as addition Eudragit® RL is more permeable while Eudragit® RS is more elastic. They are often used in different combination and ratios to obtain the suitable matrix structures and customized release profile [12].

Clay-polymer nano composite is a combination of polymer and clay as filler that has at least one dimension in the nanometer range [13, 14]. Clay-polymer nano composite was recently studied for academics and industries due to the addition of a small amount of filler in the polymer will be able to improve the mechanical properties such as elasticity and strength properties of the polymer, permeability, the heat retention properties of the polymer and also the barrier gas properties [15, 16].

Clay is a material that is often used as filler in nano composite system. It is strong, rigid, abundant in nature, easily obtained at low cost and has a high surface area (±750 m2/g). In addition, the clay has a simple structure and can be intercalated or exfoliated and chemically modified so that this system is compatible with the polymer dispersion to the nanometer scale. The material most

commonly used as the nanoclay filler is sodium bentonite (NaB). Montmorillonite as well as a member of smectite clays groups is the main constituent of bentonite. It has a colloidal structure with very small particle size and can only be identified by X-ray diffraction [17].

The objective of this experiment was to formulate the polymer-nano composite for coating grastroretentive extended release tablet. This coating was intended to maintain the bouyancy and intact of tablet.

MATERIALS AND METHODS

Instruments and materials

Instruments

Analytical weighing machine (Mettler Toledo, JL 602-GL), mixing instrument (Tubula, T2C), moisture analyzer (Metler, LJ16), flow tester (Erweka GDT), tapped density measurement instrument (Erweka, SVM 10), tablet machine (Stokes, model 592-2), hardness test instrument (Erweka, TB-24), dissolution instrument (Hanson, SR 8), UV spectrophotometer (Beckman du 650i), Universal Penetrometer (Precision Scientific), electronic stirrer (IKA RW Digital 20), water bath, Diffusion Cell kit, Conventional Pan Coater (Erweka, DKE), Ultraturax (IKA, T18 digital)and other common laboratory apparatus and glasswares.

Material

The materials used were Dipyridamole (Ruicheng County Hongqiao Pharma Middle Product Co., Ltd.), HPMC (Colorcon), PVP (ICP), lactose, Avicel PH 101 and Ac-di-sol (FMC), Sodium Bicarbonate (Merck), Citric acid (Merck), Carbopol (Lubrizol), Magnesium Stearat and Talc (Merck), anhydrous ethanol (Merck), Eudragit® RS 30D and Eudragit® RL 30D (Evonik), PEG 600 (Merck), Sodium Bentonite (Sud Chimie Indonesia).

Methods

Preparation of bentonite magma

Bentonite magma was prepared by mechanical means using the blender. Hot purified water of 125 g was placed in the blender and while the machine was running, 15 mg of bentonite was added. Hot purified water was added to make up 250 g. The mixture was allowed to stand overnight.

Preparation of polymeric film

An aqueous colloidal polymethacrylate dispersion, Eudragit® RL 30D, Eudragit® RS 30D and PEG 6000 (based on dry polymer weight) was stirred using a magnetic stirrer for 30 minutes. Certain amount nano composite bentonite magma based on dry polymer weight was added to the suspension (table 1). The dispersion was then stirred with ultra-turrax at RPM 8000 for 15 minutes. The polymeric films were prepared by casting the resulting suspension onto the Teflon sheets mounted on a leveled glass plate. The films were dried and the dried films were peeled from the Teflon surface and further used for mechanical properties test and other evaluations.

Table 1: Formulation of polymeric film

Composition	Formulation															
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Eudragit® RL 30 D (%)	50	40	30	20	50	40	30	20	50	40	30	20	50	40	30	20
Eudragit® RS 30 D (%)	50	60	70	80	50	60	70	80	50	60	70	80	50	60	70	80
PEG6000 (w/w %)	10	10	10	10	20	20	20	20	10	10	10	10	20	20	20	20
Composite (Clay)	-	-	-	-	-	-	-	-	2	2	2	2	2	2	2	2

Evaluation of polymeric film

Identifying minimum film forming temperature (MFT)

MFT was determined by preparing polymer film as the formulation in (table 1) and dried in oven with different temperatures. The stored temperatures were 60°C, 50°C, 40°C and room temperature for 12 hours.

Evaluation of mechanical properties

The mechanical properties of the films were measured by a puncture test using Penetrometer. A probe with spherical ends (diameter 4 mm) was driven through the dry film. Force-displacement values were recorded with a 1.5-N load cell. The load at the break and the maximum displacement of the film samples was measured, and then converted into puncture strength (MPa) and elongation at the puncture (%). The puncture strength and the % elongation were calculated using the following equations.

$$Puncture\ Strength = \frac{F}{Acs}$$

Where F is the load required for puncture, Acs = 2rS, where r is radius of the hole and S is the thickness of the film

$$\%\ \text{Elongation} = \frac{\sqrt{r^2 + D^2} - r}{r} \times 100$$

Where r is radius of the film exposed in the cylindrical hole of the instrument, D is the time taken for the film to puncture when the load is released.

Evaluation of drug diffusion in film

The diffusive ability of film was evaluated using Diffusion Cell kit. 50 ppm solution of dipyridamole in HCl 0.1 N was placed in a compartment in the Diffusion Cell kit followed by film membrane on top. 0.1 N HClwas placed in a beaker as the aceptor medium. The temperature of Diffusion Cell and acceptor medium was maintained at a temperature of 37.0 C. The acceptor medium was mixed at a rotation of 50 RPM. The aliquot (5 ml) was withdrawn in 15, 30 and 45th minutes, followed by 1, 2, 3, 4, 5, 6, and 7th hour. The samples were filtered with 0.45um membrane filter. The concentration of dipyridamole diffused through the membrane into the acceptor medium of HCl 0.1 N was measured using a UV spectrophotometer at the wavelength of 282 nm.

Formulation of core tablet

The model tablet was prepared by a wet granulation method using dry ethanol and formulated to meet some requirement for gastro retentive tablet. Based the formulation development activity (data not published), it would take a formulation which meets closely to the gastro retentive tablet requirement. The tablet made up by PVP 10%, HMPC 10%, Avicel PH 101 qs, Ac-Di-Sol 3%, sodium carbonate 5, 45%, citric acid 4, 55% as internal phase and Ac-Di-Sol 2%, Carbopol 5%, Mg stearate 1%, Talc 2% as external phase.

Tablet evaluation

Tablet evaluations entail of weight variation and shape of the tablet, hardness, friability, frictibility, active ingredient content and also dissolution test. While informal test such as the floating capacity of tablet also conducted during the experiment.

Dissolution test

Dissolution test of dipyridamole tablet was carried out with type 2 (spindle) apparatus at the speed of 50 RPM in the medium of HCL 0.1 N, 900 ml at 37.0±0.5 °C for 8 hours. Aliquot of 10 mL was withdrawn at 30th minutes, an hour, 2, 3, 4, 5, 6, 7 and 8th hour. The amount of dipyridamole dissolved was determined using a UV spectrophotometer at a wavelength of 282 NM.

The required dose for dipyridamole and its release from tablet were calculated using the equation of Do=Ct. td. Cl [18]. Do, Ct, td and Cl were pharmacokinetic parameters of the drug such as the therapeutic concentration, drug elimination and also the desired duration of the drug to work respectively. Dipyridamole gives therapeutic effect on plasma concentration of 0.5-1.9 µg/ml. The total clearance of dipyridamole is 2.3-3.5 ml / minutes per kg bw. The dose of sustained release dipyridamole tablet which desired to work for 8 hours, which is in the range of the dose is 50 mg.

Table 2: Release requirement of dipyridamole

Time	Amount of dipyridamole dissolved	% of dipyridamole dissolved	% drug release requirement
Release at 4th hour	19.32 – 29.40 mg	38.64 – 58.80	40 – 60 %
Release at 8th hour	38.64-58.80 mg	77.28 – 117	>80 %

Floating capacity

The *in vitro* buoyancy was determined by floating lag times. The tablets were placed in a 100 ml beaker containing 0.1 N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time. The experiments were conducted in triplicate. Total floating times were measured during *in vitro* dissolution studies.

Coating of the core tablet

After obtaining suitable formulation for both floating tablet and film, the core tablets were then coated using the Conventional Pan Coating Instrument. The following formulation was calculated for 100g spray suspension with 4 % weight gain per tablet. 300 g tablets are weighed for the coating process.

Table 3: Formulations of coating

Ingredients	Quantity based on dry polymer (%)	Quantity to be weighed (g)		Dry substance (g)
		F1	F2	
Eudragit®RS 30D		32.0	32	9.6
Eudragir®RL 30D		8.0	8.0	2.4
PEG 6000	20	2.4	2.4	2.4
Sodium Bentonite	2	4.0	-	0.9
Water		53.6	57.6	-
Total		100.0	100.0	15.3

Eudragit® RL 30D and Eudragit® RS 30D were mixed together and stirred manually using a glass rod for 5 minutes. PEG 6000 was added and stirred using a magnetic stirrer for 15 minutes prior to an appropriate dilution and homogeneity. The nano-composite bentonite magma was added to the dispersion solution. The solution was then stirred with ultra-turax at RPM 8000 for 10 minutes. The dispersion was continuously stirred and water added up to 100g.

300 grams of tablets were rotated at the speed of 10-20 RPM on the pan coater. The atomization air pressure was set at 4 bar with spraying speed of 3g per minute. The distance of the nozzle was 10 to 15 cm from the tablets. The inlet temperature was 50°C and the product temperature was maintained at 40°C. The coated tablets that obtained were then evaluated with required evaluations.

Evaluation of coated tablet

Coated tablet was evaluated involving floating properties and dissolution of dipyridamole from its tablet.

Table 4: Results of organoleptic test and FMT determination of polymeric film

Formulation															
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
The film cracking observed at drying temperature of 60, 50, 40˚C and room temperature				Well-formed film at all drying temperatures except cracking observed at room temperature				The film cracking observed at drying temperature of 60, 50, 40˚C and room temperature				Well-formed film at all drying temperatures except cracking observed at room temperature			

RESULTS AND DISCUSSION

Preparation and evaluation of polymeric film

Preparation of polymeric films was started by preparing the polymer dispersion to identify the amount of plasticizer needed and to identify the minimum film forming temperature of the dispersion (table 1). The percentages of plasticizer used were 10 and 20%, while the percentage of nano composite was 2% (w/w dry clay) based on dry polymer weight.

The ratio of the Eudragit® RL 30D and Eudragit RS 30D as polymers were selected based on the desired release properties. Eudragit® RL 30D increases the initial drug release more significantly while the Eudragit® RS 30D minimize the initial drug release, but increases the terminal drug release more significantly [19].

It was found that the film formulation containing PEG 6000 of 20 % (formula 13, 14, 15 and 16) dried on drying temperature of 40°C or above, formed a solid film without any crack and damage on the surfaces, while the film formulation containing 10% plasticizer were too brittle and underwent cracking and less homogeny surface at all drying temperature used. It could take the conclusion that the minimum film forming temperature was 40°C and the percentage of plasticizer that will be used for further film preparation was 20%. The formulation 5, 6, 7, 8, 13, 14, 15 and 16 were then evaluated of its mechanical properties involving elongation and puncture test.

It showed that the percent elongation of film containing Eudragit® RS 30D of 50, 60, 70 and 80% at PEG 6000 concentration of 10% were 2.14, 3.03, 3.45 and 5.87, while at PEG 6000 concentration of 20% were 3.54, 4.12, 5.23 and 7.08 respectively (table 5). It was found that the increment of Eudragit® RS 30D content increased the percentage of elongation. It suits the characteristics of an Eudragit® RS 30D, which was more elastic. The results of puncture strenght test of formulation which didn't contain nano composite, formula 5, 6, 7 and 8 were 0.625, 0.536, 0.441 and 0.385, while which contained nano composite, formula 13, 14, 15 and 16 were 0.617,

0.517, 0.405 and 0.346 Mpa respectively. At the same ratio, it was found that the result of puncture test from formulation which didn't contain nano composite was more than a form which contained nano composite such as the value of formula 8 (0.385)>formula 16 (3.46). It showed that the formulations with nano composite gave rise to the strength of the polymer film. The rationales for the selection were based on the results of the mechanical properties test as it showed those formulations that were suitable to be used as coating layer. For further evaluation, we choose formulation 8 (without nano composite) and 16 (with clay) that contained Eudragit® RS 30D and Eudragit® RL 30D in a ratio of 80:20.

Table 5: Mechanical properties of polymeric film

Evaluation	Formulation							
	5	6	7	8	13	14	15	16
Puncture Strength (MPa)	0.625	0.536	0.441	0.385	0.617	0.517	0.405	0.346
% Elongation	2.14	3.03	3.45	5.87	3.54	4.12	5.23	7.08

As the search for the optimum polymeric film formulation continues, we endure the evaluation towards diffusion test for the chosen formulations. The diffusion ability of polymeric film was evaluated to identify the ideal formulation for the coating process. As our main objective to control-release the drug and increases the residence time of the tablet in the stomach, we need to consider the release profile of dipyridamole through the membrane and the ability of the film to assure the strength of the film.

The results showed that the percentage of dipyridamole passed through the film of formulation 8 and 16 was superimposed during the 7 first hours and after 7 hours, they split in which the formulation 8 was higher than formulation 16. Formulation 8 and 16 showed a delay in the initial drug release, but it increased after 3 hours of the test and it complied with zero order kinetic which was similar to the calculation of dose and release (fig. 1).

Hence, the two polymeric film formulations were used in the coating process to compare the effect of nano composite towards the film ability and drug release.

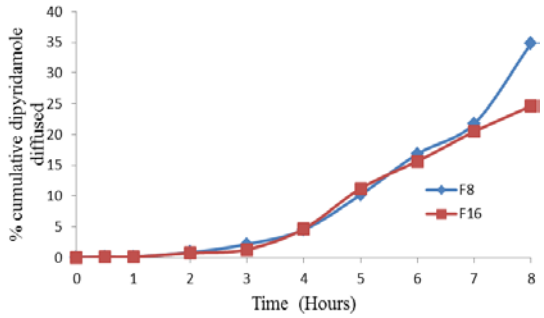

Fig. 1: Percentage of dipyridamole diffused through film F8 and and F16

Core tablet formulation, coating and its evaluation

Wet granulation method was used to prepare the core tablet of dipyridamole sustained-release tablet. We used anhydrous alcohol to dissolve the polyvinlypyrilidone which act as a binder and prevent acid-base reaction of sodium carbonate and citric acid. The model formulation used was Avicel PH 101 as filler because it has a low density and can increase the buoyancy. Carbopol in the external phase and HPMC in the internal phase where both act as the swellable polymer.

It formed hydrocolloid gel by swelling first as it got contact with the medium earlier and prevents the release of carbon dioxide as a result of sodium carbonate and citric acid reaction. Carbopol at the external phase control the water uptake into the tablet matrix. Even though carbopol erode as time increases, the presence of HPMC at the internal phase still can control release and give buoyant to the tablet [9]. The coating process was conducted using a suitable polymeric film formulation of 8 and 16.

From the evaluations, we did observe that the tablet coated had gained weight roughly around 4-5 % (table 6). After coating, the hardness of the tablet increases, as it reached nearly 8-10 kg/cm for both the formulations. Further, the tablets were evaluated for floating lag time. It showed that the core tablet had the floating lag time of 4 seconds, which were even shorter than others (data not published). The tablet coated without nano composites showed average of 7 seconds lag time.

While the tablet coated with 2% nano composites showed an average of 1 minutes 53 seconds lag time (table 7). This may be due to the presents of nano-particles inhibited the diffusion of the medium into the membrane. The medium entering will directly contact with the swelling and gas generating agent in the core tablet and it made the tablet to float.

Table 6: Evaluation of core and coated dipyridamole tablet

Evaluation	Core tablet	Eudragit® RS 30D/ RL 30 D (8:2) and 20% PEG 6000	Eudragit® RS 30D/ RL 30 D (8:2) and 20% PEG 6000 with 2% nano-composite
Weight (mg)	503.21±2.45	514.34±7.39	524.87±10.21
Friability (%)	0.84	0.19	0.14
Frictibility (%)	0.45	0.23	0.15
Hardness (kg)	8.35±0.41	8.35±1.61	9.25±1.23

Table 7: Floating lag-time of dipyridamole coated tablet

Tablet		Coated tablet	
	Core tablet	Eudragit® RS 30D/ RL 30 D (8:2) and 20% PEG 6000	Eudragit® RS 30D/ RL 30 D (8:2) and 20% PEG 6000 with 2% Nano-composite
1	0':03"	0':08"	2':31"
2	0':02"	0':05"	1'.35"
3	0':07"	0':08"	1':43"
Average	0':04"	0':07"	1':53"

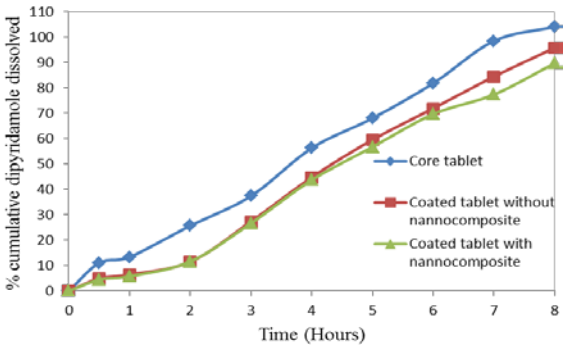

Fig. 2: Dissolution profile of dipyridamole

It was found that the formulation without nano-composite which consisted of Eudragit® RS / RL 30D in a ratio of 80:20 and 20 % PEG 600 (w/w dry polymer) gave 44.76±4.74 % of release at 4th hour and 95.76±1.35 % at 8th hour. While the formulation with nano composite of 2% along with the polymer dispersion gave 43.59±3.59 % release at 4th hour and 89.69±4.92 % of release at 8th hour. Release studies of dipyridamole coated floating tablets showed that both coated layer gave release upon the requirement that needed for a sustained-release dipyridamole floating tablet. The result dissolution complied with the zero order release and was similar to the release order calculated during the determination of the requirement.

Even though the both formulations of thin layer film meet the requirement of release, in order to control the release of dipyridamole, the tablet needs to float on the stomach medium for at least 8 hours. During the release studies, we did the floating capacity evaluation towards the both coated tablet formulations (table 8).

The medium diffusion in the matrix of core tablet was capable of solvation of the polymer and slowly collapsing the entrapped air from the matrix. This leads to the gradual loss of floating behavior for the core tablet. Even though the formulation meets the requirement of the release earlier than expected, the formulation chosen still favors ahead of the other formulas to be the core tablet in the coating process of dipyridamole controlled release tablet.

It was clearly understood that the film formulation without nano-composite loses its floating effect towards the end of the dissolution studies; this may be due to the retardation of the polymer due to the swelling effect of the polymer in contact with the medium. It leads to the solvation of the polymer and slowly collapsing the entrapped gas within the film while formulation using nano-composite, gaves good mechanical strength towards the film. This can be noticed as the entrapped gas from the effervescent system trapped within the solid layer of the film and gave the buoyant effect of the tablet until the 8th hour. This was clearly agreeable as, the presents of nano-composite clay, sodium bentonite in the polymer dispersion to form film, will reduce the gas permeability and increases the mechanical strength.

Table 8: Floating capacity of the dipyridamole coated tablet

Tablet	Formulation		
	Core tablet	Eudragit® RS 30D/ RL 30 D (8:2) and 20% PEG 6000	Eudragit® RS 30D/ RL 30 D (8:2) and 20% PEG 6000 with 2% Nano-Composite
1	5':34':03"	6':57':50"	>8':00':00"
2	6':25':00"	6':43':58"	>8':00':00"
3	6':08':05"	7':33':07"	>8':00':00"
Average	5':54':46"	7':08':27"	>8':00':00"

CONCLUSION

The studies showed that the formula of polymeric film that contains Eudragit® RS / RL 30D with the ratio of 80:20 and PEG 6000 20% (w/w dry polymer) as plasticizer with the presence of nanoclay, sodium bentonite 2% (w/w dry clay) together with expanding and effervescent system of the core tablets convey tablet that floats for 8 hours and produce the release as 43.59±3.59 and 89.69±4.92 at 4th and 8th hour respectively and met the requirement that has been set.

CONFLICT OF INTERESTS

Declared None

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