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Formulation development and evaluation of bilayer tablets of sucralfate and amoxycillin for the effective treatment of ulcer

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Abstract

Objective: The present research was carried out with the aim of developing bilayer tablets of sucralfate and amoxycillin for the effective treatment of ulcer.

Methods: Development of bilayer tablet of sucralfate and amoxycillin was carried out by the direct compression method. Finally it was optimized according to several evaluation parameters.

Results: Based on the cumulative dissolution studies of sucralfate and amoxcillin similarity factor and other physical evaluation studies, the IF8 and F8 formulation were present exhibited good properties of bilayer tablet formulation in terms of excipient proportion. Formulate instant release layer and control release layer individually passed the pre-compression tests that are angle of repose, bulk density, tapped bulk density, compressibility index, and hausner's ratio. The instant release layer of released approx 99.89 percent of drug within 15 min and control release layer released approx 99.89 percent of drug up to 12 hrs.

Conclusion: Experiment concluded that bi-layer tablet is suitable for delivering same drugs with different release pattern like one layer of drug as immediate release to get quick relief from pain and second drug as sustained release of drug which gives effect of drug for sufficient long time and reduce frequency of dose.

Keywords: Sucralfate, Amoxicillin, Bilayer tablets, Ulcer.

Introduction

The goal of any drug delivery system is to provide a therapeutic amount of the drug to the proper site in the body to achieve promptly, and then maintain the desired drug concentration [1]. The layered tablet concept has been utilized to develop controlled-release formulations [2-7]. Such a tablet is considered as a biphasic delivery system that is designed to release the drug at two different rates and is usually composed of a fast release layer combined with single [2-5] or double sustained-release layers [6,7]. Generally, conventional controlled-release dosage forms delay the release of drugs and do not provide a rapid onset of action after oral administration [8, 9]. Hence, the layered tablets offer a pharmacokinetic advantage over conventional controlled-release dosage forms as the drug is quickly released from the fast-release layer leading to rapid rise of drug plasma concentration followed by continuation of drug release from the sustained release layer [9]. This release pattern is required for successful treatment in many therapies, primarily when maximum relief needs to be achieved as soon as possible, and is followed by a sustained-release phase to avoid repeated drug administration.

The present research was carried out with the aim of developing bilayer tablets of sucralfate and amoxycillin for the effective treatment of ulcer. Sucralfate, the basic aluminum salt of sucrose octa sulfate is used in the treatment of peptic ulcers. Sucralfate binds to the ulcerated surface by chemically complexing with the exposed protein. Since the mole cule has a high molecular weight and has eight potentially hydrolyzable alumina groups, it protects the ulcerated surface from contact with the stomach acid and pepsin, thus reducing the immediate discomfort and facilitating the healing process [10]. Sucralfate is a locally acting substance that in an acidic environment (pH < 4) reacts with hydrochloric acid in the stomach to form a cross-linking, viscous, paste-like material capable of acting as an acid buffer for as long as 6 to 8 hrs after a single dose. Amoxicillin is a semi-synthetic aminopenicillin, with a broad-spectrum bactericidal activity [11-15], used as trihydrate in oral products. Amoxicillin trihydrate is likely a white or almost white crystalline powder and it is well absorbed when given orally, with a bioavailability that appears to be much higher than expected based on its physicomechanical and biopharmaceutical properties, and the pH partition theory.

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Materials and methods

Materials

All other reagents and chemicals used were of analytical reagent grade.

Methods

Development of bilayer tablet of sucralfate and amoxycillin was carried out by the direct compression method. Finally it was optimized according to several evaluation parameters [16].

Formulation development

Prepration of instant layer of sucralfate

Fast dissolving tablets of sucralfate were prepared by direct compression method after incorporating different superdisintegrants such as, crosscarmellose sodium (Ac-Di-Sol), crospovidone and sodium starch glycolate in different concentrations. The ingredients given in table 1 were weighed and mixed in geometric progression in a dry and clean mortar. Then the ingredients were passed through mesh #60. Magnesium stearate as lubricant and talc as glidant were added in a final step and mixed, this blend was subjected to analysis of pre-compression parameters which included angle of repose, bulk density, tap density, carr's index and hausner's ratio. The blend was compressed on 8 mm (diameter) fat punches on a Rimek mini press 16 station rotary compression machine. Eight formulations of sucralfate granules were prepared and each formulation contained one of the three disintegrant in different concentration. Each tablets weighing 100 mg, were obtained. Compositions of tablets are mentioned in table 1.

Table 1: Composition of sucralfate fast dissolving tablets

Ingredients(mg)	Formulation code								
	IF1	IF 2	IF 3	IF 4	IF 5	IF 6	IF 7	IF 8	IF 9
Sucralfate	200	200	200	200	200	200	200	200	200
Sodium starch glycolate	5	7.5	10	_	_	_	_	_	_
Croscarmellose sodium	_	_	_	5	7.5	10	_	_	_
Crospovidone	_	_	_	_	_	_	5	7.5	10
Microcrystalline cellulose	34	31.5	29	34	31.5	29	34	31.5	29
Talc	5	5	5	5	5	5	5	5	5
Magnesium stearate	6	6	6	6	6	6	6	6	6
Total weight	250	250	250	250	250	250	250	250	250

Evaluation of post compression parameter

Shape and colour of tablets

Uncoated tablets were examined under a lens for the shape of the tablet and colour was observed by keeping the tablets in light.

Thickness test

Three tablets were picked from each formulation randomly and thickness was measured individually. It is expressed in mm and standard deviation was also calculated. The tablet thickness was measured using dial-caliper (Mitutoyo, Japan).

Weight variation test

Twenty tablets were selected randomly from each formulation and average weight was determined. The tablets were weighed individually and compared with average weight.

Hardness test

The hardness of tablet was measured by Pfizer hardness tester and results were expressed in Kg/cm^2.

Friability test

For this, 20 tablets were taken from each formulation and the friability was determined using Roche friabilator. The equipment was run for 4 min at 25 revolutions per min. The tablets were taken out, dedusted and reweighted and % friability was calculated. The friability was determined as the mass loss in percent according to equation:-

$$\%Friability = (Loss\ in\ weight/Initial\ weight) \times 100$$

Uniformity of drug content:

The test is mandatory for tablets with 10 mg or less weight of active ingredient. Ten randomly selected tablets from each formulation (F1 to F9) were finely powdered and drug equivalent to 10 mg of drug was dissolved in 10 ml 0.1 N HCl (simulated gastric fluid of pH 1.2 without enzymes) and sonicated it for 20 min, till the entire drug leached out from complex, then the solution was filtered through whatman filter paper No. 41. From this solution 1 ml was diluted up to 100 ml with 0.1 N HCl and the drug content was determined spectrophotometrically at 238.0 nm.

Method for preparation of amoxicillin floating tablet

Direct compression method was followed to manufacture the gas generating floating tablets of amoxicillin. Nine different formulations (F1, F2, F3, F4, F5, F6, F7, F8, & F9) were prepared by direct compression. All the polymers selected

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(HPMC K 15, HPMC K 4 and PVP K 30), drug and excipients were passed through sieve no. 40 before using into formulation. The amount and ratio of drug and polymers were weighed as per given in table 2 and all the formulation were used for further evaluations parameters.

Table 2: Various formulations of amoxicillin gastro retentive floating tablets

Excipients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Amoxicillin	250	250	250	250	250	250	250	250	250
HPMC K 15	_	_	_	160	170	180	80	85	90
HPMC K 4	160	170	180	_	_	_	80	85	90
PVP K30	15	15	15	15	15	15	15	15	15
Citric acid	5	5	5	5	5	5	5	5	5
$NaHCO_3$	20	20	20	20	20	20	20	20	20
$Mg(C_{18}H_{35}O_2)_2$	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5
Lactose	40	30	20	40	30	20	40	30	20
Total Weight	500	500	500	500	500	500	500	500	500

All the tablets were evaluated for general appearance, thickness and diameter, drug content and dissolution rate studies [16]. For the determination of drug content twenty tablets were taken and amount of drug present in each tablet was determined. The tablets were crushed in a mortar and the powder equivalent to 100 mg of drug was transferred to 100 ml standard flask. The powder was dissolved in 50 ml of 0.1 N HCl and made up to volume with of 0.1 N HCl. The sample was mixed thoroughly and filtered through a 0.45µ membrane filter. The filtered solution was diluted suitably and react with dye and analyzed for drug content by UV spectrophotometer at a λ-max of 238.0 nm using of 0.1 N HCl as blank.

In vitro drug release of the sample was carried out to determine the dissolution rate using USP- type II dissolution apparatus (Paddle type). The dissolution medium, 900 ml 0.1N HCl was placed into the dissolution flask maintaining the temperature of 37±0.5 °C and rpm of 75. One amoxicillin tablet was placed in each basket of dissolution apparatus. The apparatus was allowed to run for 10 hrs. Sample measuring 5 ml were withdrawn after every 1 h up to 10 hrs using 10 ml pipette. The fresh dissolution medium (37 °C) was replaced every time with the same quantity of the sample. From this 0.5 ml was diluted up to 10 ml with 0.1 N HCL. 2 ml of this solution was taken and 1 ml of methyl orange followed with chloroform was added and lower layer was collect to take the absorbance at 238.0 nm using spectroscopy.

Formulation development of bilayer tablet

Optimized formulation IF-8 of Instant release layer and optimized formulation of F-8 for control release used for formulation of Bi-layer tablet. All the tablets were evaluated for general appearance, thickness and diameter, friability, uniformity of weight, drug content and dissolution rate studies [16].

For drug content estimation twenty tablets were taken and amount of drug present in each tablet was determined. The tablets were crushed in a mortar and the powder equivalent to 10 mg of amoxicillin was transferred to 10 ml standard flask. The sample was mixed thoroughly and filtered through a 0.45µ membrane filter. The filtered solution was further diluted 0.1 ml to 10 ml suitably (10 ppm of amoxicillin) and individually prepared 10ppm solution of amoxicillin to determine the concentration of drug using 238.0 nm.

In vitro drug release was performed to evaluate dissolution rate according to the USP dissolution apparatus II at 50 rpm and 37±0.5 ºC temperature over a 12 hrs period for amoxicillin and 1 h for sucralfate IR, using an automated paddle dissolution system (Labindia). A minimum of 6 tablets per batch were tested. The media used was 0.1N HCl at a pH 1.2 and a volume of 900 ml was maintained at 37±0.5 °C. Test sample (1ml) was withdrawn at particular time interval and replaced with fresh dissolution media maintained at the same temperature and the concentration of dissolved drug was determined using U.V. (Ultraviolet Labindia 3000+) spectrophotometer at λmax 238 nm.

Results and discussion

Fast dissolving tablets of sucralfate were prepared by direct compression method and were subjected to analysis of pre-compression parameters which included angle of repose, bulk density, tap density, carr's index and hausner's ratio. The results are tabulated in table 3. The results of evaluation of post compression parameters are tabulated in table 4.

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Table 3: Results of pre-compression parameters of sucralfate

Formulation code	Parameters				
	Loose Bulk density(gm/ml)	Tapped bulk density(gm/ml)	Carr's Index (%)	Hausner's Ratio	Angle of Repose
IF1	0.33	0.43	23.255	1.303	40025
IF2	0.32	0.44	27.272	1.375	41025
IF3	0.31	0.45	31.111	1.452	41036
IF4	0.33	0.45	26.666	1.364	42026
IF5	0.30	0.41	26.829	1.367	43015
IF6	0.30	0.42	28.571	1.400	43036
IF7	0.32	0.43	25.581	1.344	41056
IF8	0.31	0.44	29.545	1.419	41026
IF9	0.34	0.45	24.444	1.324	40023

.Table 4: Results of post-compression parameters of all formulations

Formulation code	Hardness test (kg/cm^2)	Friability (%)	Weight variation (%)	Thickness (mm)	Drug content (%)	*In vitro* Disintegration Time (min.)
IF1	3.13 ± 0.21	0.8217± 0.01	250.15±2.3	1.42 ±0.03	99.41±0.42	3.48±0.56
IF2	3.70 ± 0.30	0.7262 ±0.05	255.12±3.4	1.45 ±0.05	99.77±0.51	6.40±0.71
IF3	3.51 ± 0.50	0.5314 ±0.03	254.15±2.5	1.41 ±0.03	98.53±0.71	5.34±0.41
IF4	3.73 ± 0.29	0.6425 ±0.11	249.78±1.8	1.40±0.06	99.41±0.49	8.00±0.22
IF5	3.81 ± 0.51	0.6346 ±0.05	252.45±5.4	1.44 ±0.03	99.33±0.66	6.34±1.23
IF6	3.50 ± 0.40	0.7114 ±0.16	256.36±4.6	1.46 ±0.05	98.51±0.75	1.50±1.53
IF7	3.66 ± 0.29	0.5612 ±0.07	251.78±4.2	1.40 ±0.04	99.57±0.42	1.54±0.96
IF8	3.77 ± 0.71	0.8554 ±0.11	250.12±4.3	1.43 ±0.05	98.33±0.62	1.03±0.69
IF9	3.12± 0.42	0.7377 ±0.15	253.13±2.4	1.42 ±0.04	99.65±0.48	2.45±1.15

(n=3); Mean ± SD

Direct compression was followed to manufacture the gas generating floating tablets of amoxicillin. Results of pre-compression properties of amoxicillin the gas generating floating tablets are tabulated in table 5, results of post-compression properties of amoxicillin the gas generating floating tablets are tabulated in table 6 and results of *in-vitro* buoyancy study of amoxicillin tablets are tabulated in table 7.

Table 5: Results of pre-compression properties of amoxicillin tablets

Material	Angle of repose(Degree)	Bulk density* (gm/ml)	Tapped density* (gm/ml)	C.I. *	Hausner ratio*
			Amoxicillin		
F1	30.31	0.582±0.002	0.732±0.007	27.33±0.73	0.721±0.01
F2	29.35	0.581±0.008	0.730±0.006	28.33±0.72	0.723±0.01
F3	27.82	0.576±0.002	0.728±0.005	27.30±0.68	0.720±0.01
F4	30.69	0.570±0.007	0.729±0.003	29.30±0.65	0.726±0.03
F5	28.30	0.580±0.003	0.735±0.004	30.30±0.61	0.730±0.04
F6	30.28	0.585±0.003	0.732±0.006	32.80±0.64	0.728±0.06
F7	28.46	0.582±0.004	0.742±0.003	36.24±0.70	0.720±0.03
F8	29.49	0.579±0.002	0.792±0.005	29.72±0.68	0.720±0.04
F9	30.13	0.584±0.004	0.768±0.004	28.52±0.71	0.739±0.03

*(n=3); Mean ± SD

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Table 6: Results of post compression properties of amoxicillin tablets

Formulation	Thickness	Hardness	Weight variation	Friability (%)	Drug content (%)	Total floating
F1	3.53±0.05	4.8	850.19± 2.94	0.58 ± 0.10	98.33± 0.92	8
F2	3.94± 0.10	4.4	850.18 ± 3.77	0.51 ± 0.08	97.20 ± 0.34	10
F3	3.96± 0.05	4.5	850.33 ± 1.50	0.38 ± 0.12	99.60 ± 1.39	>12
F4	3.95± 0.05	4.7	852.30 ± 3.30	0.16 ± 0.04	98.14 ± 1.69	>12
F5	3.93± 0.10	5.2	853.13 ± 2.83	0.31 ± 0.07	97.21 ± 1.07	>12
F6	4.03± 0.06	5.3	849.16 ± 2.33	0.27 ± 0.05	97.50± 1.81	>12
F7	4.05± 0.05	4.8	850.18 ± 3.11	0.29 ± 0.08	98.34 ± 0.37	>12
F8	3.98± 0.05	4.5	851.04 ± 2.56	0.34 ± 0.12	98.31± 0.91	>12
F9	3.69±0.06	4.9	851.02±2.11	0.32±0.09	97.83±0.59	>12

Table 7: Results of *in-vitro* buoyancy study of amoxicillin tablets

Formulation Code	Total Floating Time (hrs)
F1	>8
F2	>10
F3	>12
F4	>12
F5	>12
F6	>12
F7	>10
F8	>10
F9	>8

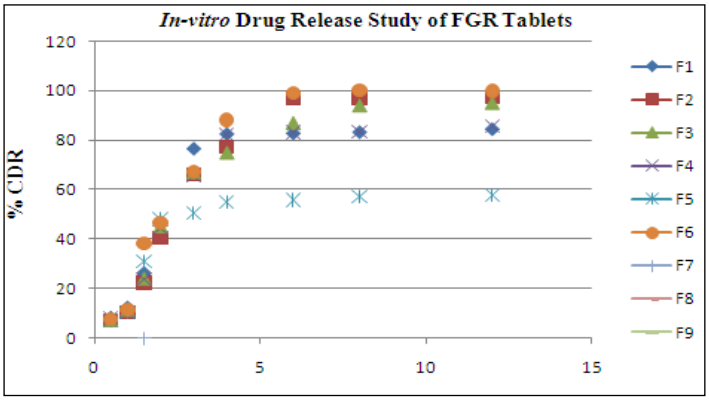

Figure 1: Results of *in vitro* drug release study of gastro retentive floating tablet

In vitro drug release of the sample was carried out using USP- type II dissolution apparatus (Paddle type) and absorbance was taken at 238.0 nm using spectroscopy. The results of *in vitro* drug release study of gastro retentive floating tablet are tabulated in figure 1. On the basis of the obtained results from pre and post-compression properties of amoxicillin release Kinetics of optimized formulation F-8 was evaluated and results are tabulated in table 8 and figure 2-5 shows the results of comparative study of regression coefficient for selection of optimize formulation F-8.

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Table 8: Release kinetics of optimized formulation F-8

Time (Hrs.)	% CDR	Log T	Root T	Log % cum. drug remain to be release	Log cum. %
0.5	7.26	-0.301	0.707	1.967	0.861
1	11.87	0.000	1.000	1.945	1.074
1.5	26.28	0.176	1.225	1.868	1.420
2	38.21	0.301	1.414	1.791	1.582
3	68.24	0.477	1.732	1.502	1.834
4	89.12	0.602	2.000	1.037	1.950
6	95.25	0.778	2.449	0.677	1.979
8	98.56	0.903	2.828	0.158	1.994
12	99.76	1.079	3.464	-0.620	1.999

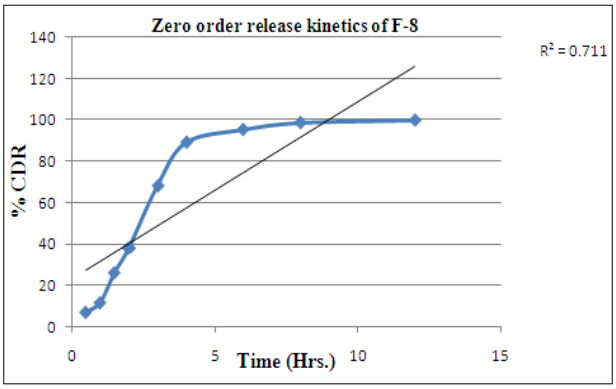

Figure 2: Graph of zero order release kinetics of F-8

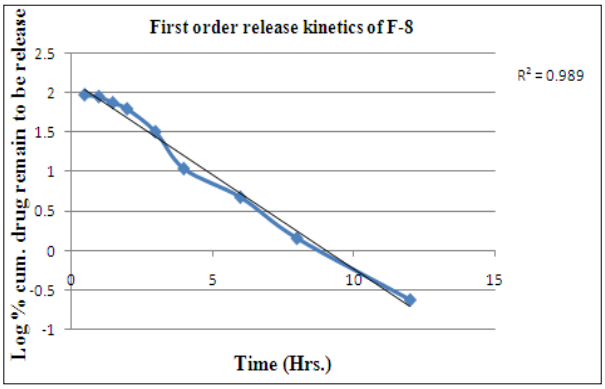

Figure 3: Graph of first order release kinetics of F-8

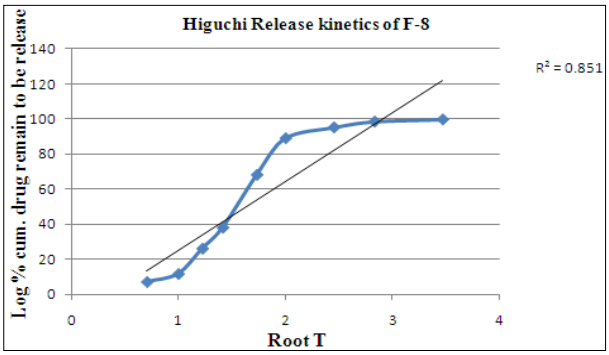

Figure 4: Graph of higuchi release Kinetics of F-8

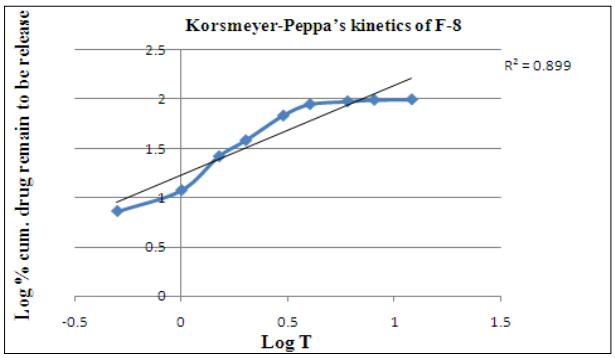

Figure 5: Graph of korsmeyer-peppa's kinetics of F-8

The *in vitro* drug release data of the optimized formulation was subjected to goodness of fit test by linear regression analysis according to zero order, first order kinetic equation, Higuchi's and Korsmeyer's models in order to determine the mechanism of drug release. When the regression coefficient values of were compared, it was observed that 'r' values of Higuchi was maximum i.e 0.989 hence indicating drug release from formulations was found to follow Higuchi kinetics.

Optimized formulation IF-8 of instant release layer and optimized formulation of F-8 for control release layer was used for formulating bi-layer tablet. The results of post-compression parameters of optimized formulation are tabulated in table 9, results following rug content are mentioned in table 10, results of dissolution rate studies of instant layer are tabulated in table 11 and results of dissolution rate studies of floating layer are tabulated in table 12.

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Table 9: Post-compression parameters of optimized formulation

Formulation code	Hardness test (kg/cm^2)	Friability (%)	Weight variation	Thickness (mm)
1.	5.65 ± 0.21	0.568± 0.01	Passes	5.56 ±0.03

Table 10: Results of drug content analysis

Formulation	Amoxicillin (% Label Claim)	Sucralfate (% Label Claim)
Bilayer floating tablet	99.15	99.23

Table 11: Results of dissolution rate studies of instant layer

Time (min)	% Drug Release of Instant layer
15	99.45 %

Table 12: Results of dissolution rate studies of floating layer

Time (Hour)	% Drug release of IR Layer	% Drug release of CR Layer
0.5	45.65	8.98
1	98.89	12.65
1.5	--	33.56
2	--	45.58
4	--	52.25
6	--	68.98
8	--	75.89
10	--	95.58
12	--	99.89

Formulating biayer tablet as instant release layer and control release layer in a bilayer tablet reduces the frequency of administration and dose of the drugs. Reduced dose of the drug automatically will tend to reduce the adverse effect of the drug. Successful bilayer tablet formulations were developed for once a day administration for treatment of ulcer. From this study by preparing bilayer tablets, it was concluded that we could reduce the total dose, dosage frequency, dose related side effects and improve the bioavailability of any drug which in turn improves the patient compliance. Thus a fixed dose combination tablet of sucralfet and amoxcillin were designed as bilayer tablets which will have good patient compliance over their individual marketed counterparts. This further confirms the integrity of pure drugs and their compatibility with the excipients.

Conclusion

The present research was carried out with the aim of developing bilayer tablets of sucralfate and amoxycillin for the effective treatment of ulcer. Bilayer tablets showed the appropriate release effect to provide the loading dose of the drug, followed by control release for 12 h, indicating promising potential of the sucralfate and amoxcillin bilayer tablet as an alternative to the conventional dosage form. However, further clinical studies are needed to access the utility of this system.

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