Formulation And Evaluation Of Floating In Situ Gel Of Eluxadoline

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Abstract

The present investigation deals with the formulation, optimization and evaluation of sodium alginate and HPMC based *in situ* stomach specific gel of Eluxadoline. Eluxadoline *in situ* gel was prepared by simple suspension method. The evaluation study shows that formulation F3 was ideally suited to the sustained release formulation. From the FTIR study and physical observation it was concluded that there was no significant Drug-Excipients interaction was observed. It was exhibited good gelling property, viscosity and pH. F3 have less floating lag time. Also F3 remain floated up to 12 hr. The promising formulations F3 have displayed good drug content and a sustain release action of 12 hrs. The controlled release of Eluxadoline was observed and good korsmeyer peppas kinetic. Based on trial batch data, 3 level 2 factor full factorial design was applied considering Sodium Alginate and HPMC K4Mas factors. Factorial batches results found satisfactory. Validation of design was done. Batch O1 found stable for 1 month during stability study. Hence, O1 is the optimized batch.

Keywords: Eluxadoline, In-Situ Gel

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INTRODUCTION

Oral route of administration is the most important and convenient route for drug delivery. Due to differential absorption from various regions of GI, the benefits of long-term delivery technology have not been fully realized for dosage forms designed for oral administration. Only recently drug delivery systems have been designed to target drugs to differential regions of GIT. These include gastro retentive systems, delayed release systems and colon targeting. The real issue in the development of oral controlled release dosage form is not just to prolong the delivery of drugs for more than 12 h but also to prolong the presence of dosage forms in the stomach or somewhere in the upper small intestine. Dosage forms with prolonged gastric residence time (GRT), i.e. gastro remaining or gastro retentive dosage form (GRDF), will bring about new and important therapeutic options [1, 2].These systems are also known as hydro dynamically balanced systems. (HBS/FDDS) They have a bulk density lower than gastric fluid (i.e. <1.004 gm/ml). The specific gravity of gastric fluid is approximately 1.004-1.010 g/cm^3 according to the "Documenta Geigy" and thus the FDDS remains buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. It is an oral dosage form (capsule or tablet) that is designed to prolong the residence time of the dosage form within the GI tract [3, 4].

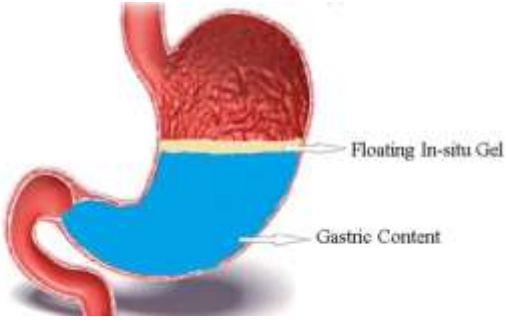

Figure 1: Schematic image of Floating In-situ Gel System

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Improvement of bioavailability and therapeutic efficacy of the drugs and possible reduction of dose e.g. Furosemide. Maintenance of constant therapeutic levels over a prolonged period and thus reduction in fluctuation in therapeutic levels minimizing the risk of resistance especially in case of antibiotics. E.g. b-lactam antibiotics (penicillins and cephalosporins) For drugs with relatively short half life, sustained release may result in a flip- flop pharmacokinetics and also enable reduced frequency of dosing with improved patient Compliance. They also have an advantage over their conventional system as it can be used to overcome the adversities of the gastric retention time (GRT) as well as the gastric emptying time (GET). As these systems are expected to remain buoyant on the gastric fluid without affecting the intrinsic rate of employing because their bulk density is lower than that of the gastric fluids. Gastro retentive drug delivery can produce prolongs and sustains release of drugs from dosage forms which avail local therapy in the stomach and small intestine. Hence they are useful in the treatment of disorders related to stomach and small intestine [5].

Eluxadoline is a mixed mu-opioid receptor agonist. Eluxadoline is a mu-opioid receptor agonist, kappa opioid receptor agonist and a delta opioid receptor antagonist. It is white to off-white solid powder. The chemical name of Eluxadoline is 5-{[(2S)-2-amino-3-(4-carbamoyl-2,6-dimethylphenyl)-N- [(1S)-1-(4-phenyl-1H-imidazol-2 yl)ethyl]propanamid] methyl}-2-methoxybenzoic acid. The molecular weight of the Eluxadoline is 569.6 g/mol. (Figure 2)

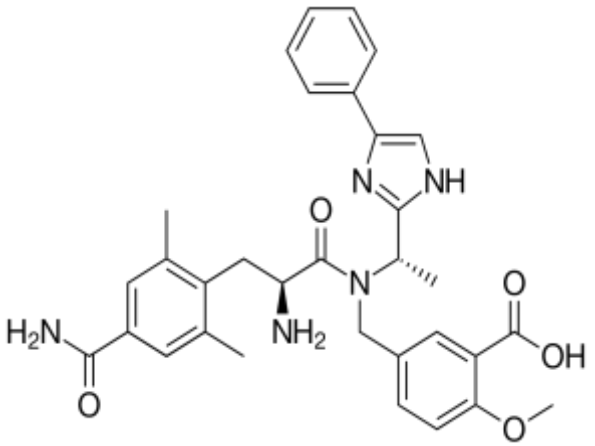

Figure 2: Structure of Eluxadoline

The metabolism of Eluxadoline is currently unclear, however evidence suggests limited glucoronidati on forms an acyl glucuronide metabolite that is then excreted into urine [10-15].

MATERIALS AND METHODS [6, 7]

Table 1: List of materials

Sr. No.	Material	Function	Sources of Material
1.	Eluxadoline	API	Astron research Ltd,Ahmedabad
2.	Sodium Alginate	Gel forming agent	SD Fine-Chemicals Ltd,Mumbai, India
3.	HPMC K4 M HPMC K100 M Carbopol 934Cellan Gum	Rate controlling polymers	SD Fine Chemicals Ltd, Mumbai, India
4.	Calcium Carbonate	Gel forming agent	SD Fine Chemicals Ltd,Mumbai, India.
5.	Methyl Paraben	Preservatives	SD Fine Chemicals Ltd,Mumbai, India.
6.	Propyl Paraben	Preservatives	SD Fine Chemicals Ltd,Mumbai, India
7.	Tri Sodium Citrate	Gel forming agent	SD Fine Chemicals Ltd,Mumbai, India

Preformulation Study:

Organoleptic Characteristics

Colour and odour of drug were characterized and recorded using descriptive terminology.

Flow Properties:

Bulk density and tapped density

Weighed quantity of the powder (W), was carefully poured into the graduated cylinder and the volume (V0) was measured. After that by tapping 100 times manually, the volume was checked and calculated from below equation.
Bulk density = W/ V0 Tapped density = W/ VF

Compressibility Index (CI) / Carr's index

Compressibility index (CI) / Carr's index was calculated by using the following formula.
% Carr's index = (T.D. - B.D. ÷ T.D.) × 100

Table 2: Relation between Carr's Index and Flow Property

(Carr's %)	Flow
5 – 15	ExcellentGood
12 – 16	Fair to passablePoor
18 – 21	Very poor Very very poor
23 – 35	
33 – 38	
>40	

Hausner's ratio

Hausner's ratio is a number that is correlated to the flow ability of a powder. It is measured by ratio of tapped density to bulk density.

Hausner's ratio = (Tapped density ÷ Bulk Density)

Angle of repose

Angle of repose of powder was determined by the funnel method. Accurately weight powder was taken in the funnel. Height of the funnel was attuned in such a way the angle of the funnel just touched the apex of the powder. Powder blend was allowed to flow through the funnel freely on to the surface. Diameter of the powder cone was

measured and angle of repose was calculated using the following equation.

Tan θ= h/r

Table 3: Relation between Angle of Repose (θ) and flow properties

Angle of Repose (θ)	Flow Properties
<25	Excellent Good Passable Very poor
25-30	
30-40	
>40	

Drug Identification and Drug-Excipients interaction study by FTIR

The Fourier transform infrared spectrum of moisture free powdered sample of pure drug and physical mixture of drug with Excipients was recorded on IR spectrophotometer by potassium bromide (KBr) pellet method. The range of spectra was found to be 600 to 4000 cm-1. The characteristics peaks of different functional group were recorded peak.

Determination of λmax and Development of Calibration Curve of Eluxadoline

Stock Solution: Eluxadoline in pH 1.2 hydrochloric acid buffer solutions.(100 µg/ml).

Scanning: From the stock solution, a suitable concentration (10µg/ml) was prepared with pH 1.2 Hydrochloric acid buffer solutions and UV scan was taken between the wavelengths of 200-400 nm and determining its λ max.

Standard Plot: From the stock solution 1, 2, 3, 4 and 5 µg/ml solutions of Eluxadoline were prepared in pH 1.2 hydrochloric acid buffer solutions. The absorbance was measured at 238 nm and a graph of concentration versus absorbance was plotted.

Dose Calculation

The total dose of Eluxadoline for a sustained release formulation was calculated by following four equations using available pharmacokinetic data from a design of one compartment model with simultaneous release of loading dose and a zero-order release maintenance dose, as described by Robison and Eriksen.

k0 = Dike (1)
Dm = k0T (2)
Dl = Di-k0Tp (3)
Dt = Dl + Dm (4)

Where,
k0 = zero order drug release;
ke = 0.693/$t_{1/2}$;
Di = initial dose/conventional dose;
Dl = loading dose;
Dm = maintenance dose;
T = time for sustained action;
Tp = time to reach peak plasma concentration;
Dt = total dose of drug;
k0 = Dike = 75 × 0.693/6 = 8.6625 mg (5)
Dm = k0T = 8.6625 × 12 = 103.95mg (6)
Dl = Di-k0Tp = 75 - (8.6625 × 2) = 57.675 mg (7)
Dt = Dl + Dm = 57.675 + 103.95=160 mg (8)

Hence the tablet should contain a total dose of 160 mg for 12 h. sustained release dosage form and it should release 57 mg in 1st hour like conventional dosage form and remaining dose (103 mg)in remaining 11 hours, Hence, the theoretical drugrelease profile can be generated using above value, which is shown in below table.

Table 4: Theoretical drug release profile

Time (hour)	Total amount of Drug releasefrom 160 mg tablet (mg)	% CPR
1	57.0	35.6
2	66.4	41.5
3	75.7	47.3
4	85.1	53.2
5	94.4	59.0
6	103.8	64.9
7	113.2	70.7
8	122.5	76.6
9	131.9	82.4
10	141.2	88.3
11	150.6	94.1
12	160.0	100.0

Method of Preparation [8, 9]

Figure 3: Method of Preparation

Formulation of In-Situ Gel of Eluxadoline Trial Batches

Table 5: Formulation of In-Situ Gel of Eluxadoline F1-F9

Materials(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Eluxadoline	160	160	160	160	160	160	160	160	160
Sodium Alginate	500	750	1000	500	750	1000	500	750	1000
HPMC K4M	250	500	750	-	-	-	-	-	-
HPMCK15M	-	-	-	250	500	750	-	-	-
HPMCK100M	-	-	-	-	-	-	250	500	750
Calcium Carbonate	1000	1000	1000	1000	1000	1000	1000	1000	1000
Tri SodiumCitrate	250	250	250	250	250	250	250	250	250
Methyl Paraben	180	180	180	180	180	180	180	180	180
Propyl Paraben	20	20	20	20	20	20	20	20	20
PurifiedWater	q.s. to 100 ml								

Table 6: Formulation of In-Situ Gel of Eluxadoline factorial batches

Materials(mg)	E1	E2	E3	E4	E5	E6	E7	E8	E9
Eluxadoline	160	160	160	160	160	160	160	160	160
Sodium Alginate	900	900	900	1000	1000	1000	1100	1100	1100
HPMC K4M	600	750	900	600	750	900	600	750	900
Calcium Carbonate	1000	1000	1000	1000	1000	1000	1000	1000	1000
Tri SodiumCitrate	250	250	250	250	250	250	250	250	250
Methyl Paraben	180	180	180	180	180	180	180	180	180
Propyl Paraben	20	20	20	20	20	20	20	20	20
PurifiedWater	q.s. to 100 ml								

Evaluation of Eluxadoline *In situ* Gel Formulation [9, 10]

Physical appearance and pH

All the formulations were visually checked for their appearance and color. The pH of the in situ solution was measured using standardized digital pH meter at room temperature by taking adequate volume in a 50 ml beaker.

Determination of Viscosity

Viscosity of the in situ gelling solution was determined with a Brookfield viscometer (Model no RVT 6513476) using a 20 ml aliquot of the sample. Measurements were performed using spindle number 2 and the temperature was maintained at 25±10C.All measurements were made in triplicate.

Gelling Capacity

The gelling capacity was determined by placing 10 ml of solution in 100 ml of stimulated gastric fluid (pH 1.2) freshly prepared and equilibrated at 37 ± 0.5°C and visually assessing the gel formation and noting the time for gelation and the timetaken for the gel formed to dissolve. Different weights were allotted as per the gel integrity, weight and rate of formation of gel with respect to time.

In vitro floating study

In-vitro floating study Floating study was carried out in 500 ml of 0.1 N HCl (pH 1.2) in a beaker. Accurately measured 10 ml of solution was added to above solution. Time requires for immersed on surface after adding solution (floating lag time) and total floating time were measured.

Determination of Drug Content

Accurately, 10 ml of in-situ gel (equivalent to 10 mg of Eluxadoline) was measured and transferred to 100 ml of volumetric flask. To this 50-70 ml of 0.1 N HCl was added and shaken on mechanical shaker for 30 min, followed by sonication for 15 min. complete dispersion of contents were ensured, visually and filtered using 0.45 µ membrane filter. From this solution, 10 ml of sample was withdrawn and diluted to100 ml with 0.1 N HCl. Contents of Eluxadoline was determined Spectro photometrically at 223 nm using double beam UV-Visible spectrophotometer.

In-vitro release studies

The drug release studies was carried out in USP II dissolution test apparatus using basket apparatus at 37 ± 0.5°C at 50 rpm using 900 ml of pH 1.2 buffer as adissolution medium (n=6). In-situ gel equivalent to 10 mg of Eluxadoline (10 ml) was used for test. 5 ml of aliquot was withdrawn at predetermined time intervals of 1 hr upto 12 hr. The contents were filtered using 0.45 µ nylon filters and analyzed at 223 nm spectrophotometrically. Same volume of dissolution fluid maintained at 37 ± 0.5°C was replaced immediately.

Drug release kinetics

Data obtained form in vitro drug release studies were fitted to disso calculation software. The kinetic models used are zero order, first order, Korshmers and pappas, Hexon crowell, and Higuchi equation. The rate and mechanism of release of the prepared films were analyzed by fittingthe dissolution data into the zero-order equation:

$Q = k0t$

Where, Q is the amount of drug released at time t, k0 is the release rate constant.

The dissolution data fitted to the first order equation:

$\ln (100–Q) = \ln 100 – K1\ t$

Where, k1 is the release rate constant.

The dissolution data was fitted to the Higuchi's equation:
$Q = K2\ t1/2$
Where, k2 is the diffusion rate constant.
The dissolution data was also fitted to Korsmeyer equation, which is often used to describe the drug release behaviour from polymeric systems:
$\text{Log } (Mt/M\infty) = \log k + n \log t$

Where Mt is the amount of drug released at time t, M∞ is the amount of drug releaseAfter infinite time, K is a release rate constant incorporating structural and geometricCharacteristics of the tablet, n is the diffusion exponent indicative of the mechanism of drug release.

Accelerated Stability Study

Optimized formulation was filled in suitable plastic container (well stoppered) bottle. Formulation was kept at suitable conditions (40 ± 2 ºC temperature and 75 ±5% RH) for 1 month. Periodically samples were removed and characterized for viscosity, drug content, *in-vitro* gelling capacity, floating lag time, total floating time and in-vitrodrug release study.

RESULTS & DISCUSSION

Preformulation Study Results

Observation of Organoleptic characteristics, flow properties and solubility of Eluxadoline are shown below Table 7, Based on below physical characterization of API it concluded that the API has a verypoor flow itself. However, in situ gel formulation does not require any flow property of API.

Table 7: Characterization of Eluxadoline

Sr. No.	Characteristic Properties		Observation/Result
1	Organoleptic Characteristics	Colour	White to off-white solid powder
		Odour	Odorless
2	Flow Properties	Bulk density (g /ml)	0.237
		Tapped density (g /ml)	0.512
		Carr's index (%)	53.41
		Hausner's ratio	2.160
		Angle of repose (θ°)	39.18°
3	Melting Point	By capillary method	180.8 °C
4	Solubility	Water	1.3 mg/ml
		0.1 HCl	1.6 mg/ml
		6.8 Phosphate buffer	1.0 mg/ml
		7.4 Phosphate buffer	1.1 mg/ml

Drug Excipient Compatibility Study by FTIR

FTIR Study of Pure drug and Formulation was done and results were reported in below figure 4. From the below results, it can be concluded that no any interaction found between drug and selected excipients.

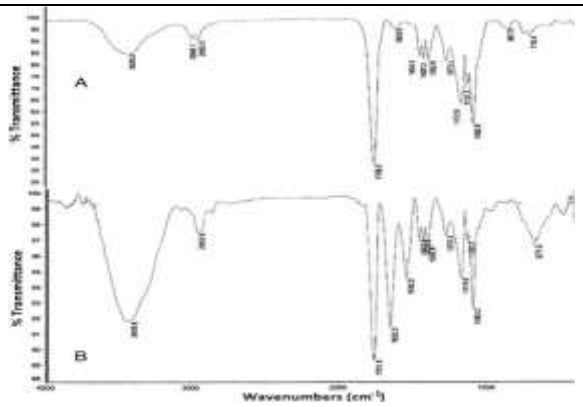

Figure 4: FTIR spectra of pure Drug and formulation A) FTIR spectra of pure Drug Eluxadoline, B) FTIR spectra of Final formulation

Table 8: FTIR Data of Drug and Formulation

Stretching	Pure Drug Peak (cm⁻¹)	Formulation Peak (cm⁻¹)
Aromatic C-H stretch	3429.2	3428.8
Aromatic C=C stretch	1620.8	1653.3
Aromatic C-N stretch	1273.1	1270.3
C-O stretch	1172.8	1174.6

Calibration curve of Eluxadoline

The calibration curve of Eluxadoline was found to over a concentration range 10-60 µg/ml. (R^2=0.999) the calibration curve is shown in Figure 5.

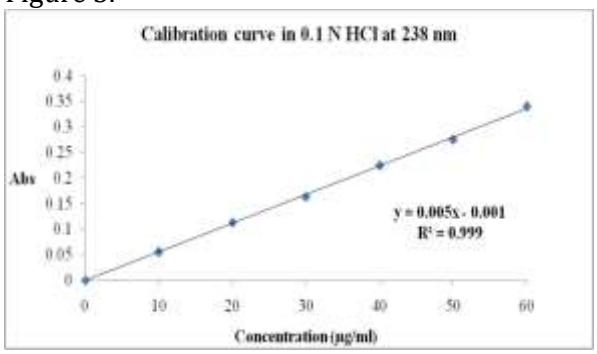

Figure 5: Calibration curve of Eluxadoline in 0.1 N HCl at 238 nm

Evaluation of In Situ Gel of Eluxadoline

Prepared formulations F1-F9 evaluated for various evaluation parameters which aregiven below Table 9 and Table 10.

Table 9: Evaluation of Formulation F1-F9

Formulation	pH	Drug Content %	Viscosity (cps)
F1	7.1 ± 0.2	99.9 ± 0.1	172 ± 5
F2	7.3 ± 0.3	99.7 ± 0.2	198 ± 4
F3	**7.0 ± 0.4**	**99.8 ± 0.4**	**201 ± 3**
F4	7.2 ± 0.2	99.9 ± 0.2	178 ± 7
F5	7.1 ± 0.4	99.7 ± 0.6	185 ± 8
F6	7.3 ± 0.1	99.8 ± 0.2	196 ± 4
F7	7.2 ± 0.3	99.4 ± 0.3	184 ± 3
F8	7.3 ± 0.2	99.7 ± 0.2	165 ± 5
F9	7.1 ± 0.3	99.5 ± 0.2	199 ± 2

Table 10: Evaluation of Formulation F1-F9

Formulation	Gelling timesec	Floating lag time(sec)	Floating Time(hr)
F1	35 ± 4	183 ± 13	5 ± 1
F2	42 ± 3	160 ± 15	7 ± 1
F3	24 ± 5	56 ± 2	12 ± 1
F4	36 ± 4	184 ± 8	7 ± 1
F5	41 ± 7	176 ± 11	8 ± 1
F6	39 ± 2	201 ± 10	10 ± 1
F7	55 ± 5	190 ± 16	8 ± 1
F8	51 ± 5	169 ± 19	8 ± 1
F9	75 ± 8	183 ± 15	10 ± 1

In Vitro drug release of F1-F9

In vitro drug release study performed for F1-F9 formulation and given in table 11. From the drug release study it concluded that only F3 formulation give drug release up to 12 hr. Remaining all release in less than 12 hr time. Further the formulation F3 profile was similar to the theoretical drug release profile. Based on that batch F3 which contains HPMC K4M polymer gives drug release up to 12 hr.

Table 11: In Vitro drug release of F1-F9

Time in hr	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	15.7± 0.1	9.3± 0.6	10.9± 0.4	15.9± 0.2	15.6± 0.6	11.8± 0.1	15.6± 0.4	10.8± 0.4	8.4± 0.4
2	36.9± 0.3	16.7± 0.7	18.5± 0.6	25.7± 0.6	24.6± 0.7	21.6± 0.2	32.7± 0.3	14.6± 0.1	16.5± 0.3
3	54.8± 0.5	30.1± 0.8	27.8± 0.6	34.4± 0.4	37.8± 0.3	36.7± 0.5	49.6± 0.3	39.7± 0.5	28.4± 0.2
4	74.3± 0.7	43.6± 0.3	34.5± 0.3	39.5± 0.7	49.4± 0.8	44.9± 0.3	69.7± 0.8	47.8± 0.6	47.2± 0.7
5	99.2± 0.9	52.4± 0.4	42.9± 0.5	51.8± 0.3	55.6± 0.5	55.7± 0.7	79.4± 0.9	65.7± 0.1	59.7± 0.8
6	-	78.9± 0.3	49.8± 0.6	69.7± 0.3	70.6± 0.8	69.4± 0.5	85.9± 0.4	74.8± 0.9	75.1± 0.1
7	-	99.7± 0.7	57.9± 0.3	90.9± 0.6	84.1± 0.3	80.9± 0.3	97.6± 0.3	86.9± 0.7	83.9± 0.4
8	-	-	66.8± 0.3	-	99.7± 0.7	89.9± 0.2	99.2± 0.1	99.7± 0.5	89.4± 0.3
9	-	-	73.8± 0.7	-	-	97.9± 0.7	-	-	93.8± 0.5
10	-	-	84.2± 0.9	-	-	99.7± 0.2	-	-	99.6± 0.4
11	-	-	90.9± 0.1	-	-	-	-	-	-
12	-	-	99.8± 0.1	-	-	-	-	-	-

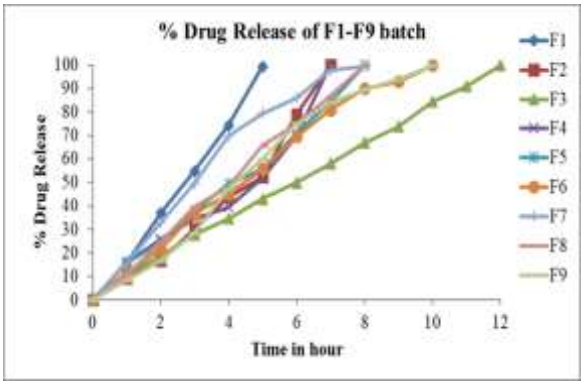

Figure 6: In Vitro drug release of F1-F9 batch

Validation of Design:

A checkpoint batch was designed accordance to the desirability function, as shown in below table. To assess the validity of prediction, a checkpoint batch C1 and C2 wasprepared and evaluated under the same conditions as outlined for the other batches. The response data was compared with that of practical data.

Table 12: Check point batch

Batch	C1	C2
Sodium Alginate (mg)	947.3	1054.5
HPMC K4M (mg)	859.8	852.
Predicted % Drug release at 1 hr	17.3	5.15
Observed % Drug release at 1 hr	17.0	5.10
% Difference	1.01	1.00
Predicted % Drug release at 8 hr	77.2	51.5
Predicted % Drug release at 8 hr	76.8	51.6
% Difference	1.00	1.00

Optimized batch:

Finally optimized batch was taken from the overlay plot and complete analysis wasdone and finally loaded for stability study.

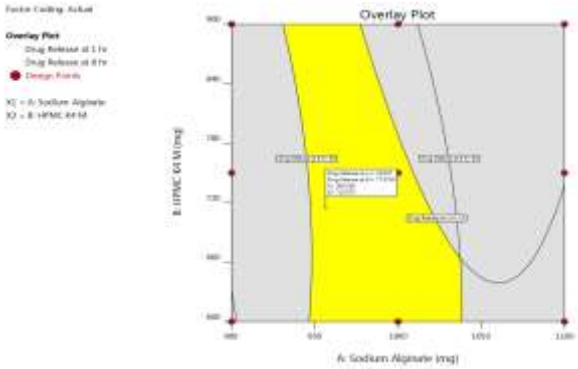

Figure 7: Overlay plot of optimized batch

Table 13: Composition of Optimized batch formulation (O1)

Materials (mg)	O1
Eluxadoline	160
Sodium Alginate	956
HPMC K4M	715
Calcium Carbonate	1000
Tri Sodium Citrate	250
Methyl Paraben	180
Propyl Paraben	20
Water	100 ml

Table 14: Results of optimized batch O1

Evaluation Parameters	Results	
pH	7.0 ± 0.1	
Drug Content (%)	99.2 ± 1.7	
Viscosity (cps)	177 ± 5	
Gelling time (sec)	36 ± 4	
Floating lag time (sec)	70 ± 7	
Floating Time (hr)	12 ± 1	
% Drug Release	Time (hr)	% Drug Release
	0	0
	1	24.9 ± 4.2
	2	40.2 ± 3.6
	4	54.5 ± 2.7
	6	68.1 ± 2.4
	8	74.9 ± 1.7
	10	87.1 ± 1.3
	12	98.9 ± 0.5

Drug release kinetic study

The drug release data of the final batch O1 was fitted in to different kinetic models. Among all, the best fitted model explained by Higuchi model because R^2 value of Higuchi model has 0.989.

Kinetic Model	Parameters	Value
Zero Order	R^2	0.933
First Order	R^2	0.731
Higuchi	R^2	0.989
Korsmeyer-Peppas	R^2	0.624
Hixon Crowell	R^2	0.908

Stability Study

Stability study of optimized batch O1 was performed for 1 month. The stability study data revealed that the O1 formulation found stable over the period of 1 month. The evaluation parameters after 1 month was found satisfactory and well within acceptable limit. The results were given in below table.

Table 15: Stability study of optimized batch O1

Evaluation Parameters	Initial	After 1 month
Appearance	Complies	Complies
Drug Content (%)	99.2 ± 1.7	99.1 ± 1.9
% Drug Release at 12 hours	98.9 ± 0.5	98.2 ± 1.6

CONCLUSION

The present investigation deals with the formulation, optimization and evaluation of sodium alginate and HPMC based *in situ* stomach specific gel of Eluxadoline. Eluxadoline *in situ* gel was prepared by simple suspension method. The evaluation study shows that formulation F3 was ideally suited to the sustained release formulation. From the FTIR study and physical observation it was concluded that there was no significant Drug-Excipients interaction was observed. It was exhibited good gelling property, viscosity and pH. F3 have less floating lag time. Also F3 remain floated up to 12 hr. The promising formulations F3 have displayed good drug content and a sustain release action of 12 hrs. The controlled release of Eluxadoline was observed and good korsmeyer peppas kinetic. Based on trial batch data, 3 level 2 factor full factorial design was applied considering Sodium Alginate and HPMC K4Mas factors. Factorial batches results found satisfactory. Validation of design was done. Batch O1 found stable for 1 month during stability study. Hence, O1 is the optimized batch.

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