Journal of Biomedical and Pharmaceutical Research
Available Online at www.jbpr.in
CODEN: - JBPRAU (Source: - American Chemical Society)
NLM (National Library of Medicine): ID: (101671502)
Index Copernicus Value 2018: 88.52
Research Article
Volume 10, Issue 2: March-April : 2021, 25-31
ISSN (Online): 2279-0594
ISSN (Print): 2589-8752

FORMULATION OPTIMIZATION AND EVALUATION OF TINIDAZOLE IN-SITU GEL

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Article Info: Received 8 February 2021; Accepted 10 March 2021
DOI: https://doi.org/10.32553/jbpr.v10i2.856
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Conflict of interest statement: No conflict of interest

Abstract
The study deals with formulation optimization and evaluation of tinidazole gel by using sodium alginate as gelling agent calcium chloride, sodium citrate were used as cross linking agent. The polymeric solution of drug is in solution form before it administered to the body. But after administration when it comes in contact with acidic pH it's converted into gel form and the drug tinidazole released from the dosage form constantly and slowly. The formulation is effective for the treatment of gastric ulcer because of Helicobacter pylori. 3^2 full factorial design were used for the optimization of the formulation 12 trial batches were prepared and 9 factorial design batches in which 2 factor 3 level factorial design were used for the optimization. The concentration of sodium alginate, were taken in 3 level low, medium, high and the prepared formulation were evaluated.
Key Words: Oral in-situ gel, Sustained Release, Prolong term of drug, Sodium alginate, Sodium citrate, Calcium chloride, Tinidazole.

1. Introduction

Helicobacter pylori (H. pylori) are reported to be an important etiologic factor in the development of the gastritis, gastric ulcer and gastric carcinoma in human stomach. H. pylori are now accepted as a cause of chronic active gastritis and are intimately associated with peptic ulcer disease. H. pylori dwell mostly in the gastric mucosa or at the interface between the mucous layer and the epithelial cells of the astral area of the stomach. A peptic ulcer are open sore that create within coating of your stomach and the upper segment of your small digestive tract in which corrosive and pepsin assume a significant job, the term is regularly used to envelop any gastric or duodenal ulceration [1][2]. The gel is defined as a soft, or semi-solid or solid like material, which has both solid and liquid component, where the solid component present as a mesh/network of aggregates, which immobilizes the liquid component. This solid network prevents the liquid from flowing by increasing the surface tension[3].In situ gels are an excellent formulation for several routes of administration. They are helpful as fluid definition in oral, effective, vaginal, and rectal organization [4].

1.1 Effect of Tinidazole on H. pylori

Improvement of H.pylori protection from tinidazole, H.pylori is found on the inward surface of the stomach epithelial cells and once in a while inside epithelial cells. It produces bonds which tie to memebrane-related lipids and starches and help it a cling to epithelial cells.
The development of in-situ gel system has received considerable attention over the past few years. In situ gel forming drug delivery is a type of mucoadhesive drug delivery system. In contrast to very strong gels they can be easily applied or used in liquid form to the site of drug absorption, where, the swell to form a strong gel that is capable of improve controldrug delivery, residence time, patient compliance.
In present study work, insitu gelling liquid formulation for sustained and control delivery of tinidazole is done because tinidazole is available in the market as tablet, capsule form. The formulation is prepared by using sodium treatment of peptic ulcer disease. The proposed alginate based formulation and in-situ gelling system of tinidazole, would have the advantage of ease of administration, as being a tablet and is more patient compliant.

2. Materials and Method

2.1 Materials

Tinidazole was received as a gift sample by Will Care PVT. LTD., Indore, sodium alginate, calcium chloride and sodium citrate was provided by Smriti College of Pharmaceutical Education laboratory. All other reagents were of analytical grade.

2.2 Method

Sodium alginate solution of concentration .5%, 1%,and 1.5% (w/v) were prepared by added the sodium alginate to ultra-pure water containing .125%,.25%,and.5% (w/v) sodium citrate and 1% (w/v) calcium chloride and heating to 60^0C while stirring. Tinidazole was dissolved in 10ml of Hydrochloric acid solution (pH1.2) and added in the resulting solution after cooling to below 40^0C. The solution was neutralized by 0.1N sodium hydroxide. A 1% (w/v) control solution (for use in the in-vitro release experiments) was prepared by dissolving Tinidazole in a 0.6% (w/v) aqueous solution of sodium alginate. A 1% (w/v) solution of Tinidazole was prepared in ultra-pure water. The resulting sodium alginate in-situ gel solution containing tinidazole was checked for viscosity and gelling property (Table 6 and 8) and finally stored in amber color narrow mouth bottles until further use. In factorial design batches G1to G9 concentration of Sodium alginate, Sodium citrate, and Calcium chloride was utilized to evaluate the responses.

Table 1: Composition of the in-situ gelling formations

Ingredients	Formulation code								
	G1	**G2**	**G3**	**G4**	**G5**	**G6**	**G7**	**G8**	**G9**
Tinidazole	100mg	100mg	100mg	100mg	100mg	100mg	100mg	100mg	100mg
Sodium Alginate	.5	.5	.5	1	1	1	1.5	1.5	1.5
Sodium Citrate	.125	.25	.5	.125	.25	.5	.125	.25	.5
Calcium Chloride	1	1	1	1	1	1	1	1	1
Distilled water	20	20	20	20	20	20	20	20	20

2.3 Experiment Design

A full factorial design experiment was conducted to study the effect of two factor, namely; the sodium alginate (X_1) sodium citrate (X_2) concentration, each at three levels (0.5,1.0,1.5%), and (.5, .25, .125 %), respectively. This gave 3^2 = 09 formulae. The responses were the drug content, percentage drug released at 5 hrs. (Q_{50}) and 8 hrs.(Q_{80}). The assigned number for each formula and the typical design of the factorial experiment are shown in Table 1. All experiment data were analysed statistically according to the established factorial design using Excel (Microsoft software).

Table 2: In-situ gel of primarily trial batch

Batch No.	Concentration of sodium alginate (%)	pH	Viscosity (cp)*	Drug content (%)*	Characteristic of in situ gels
G1	0.25	7.3	171.1	95.10	No gel formation
G2	0.25	7.3	186.3	92.18	No gel formation
G3	0.25	7.2	193.7	88.74	No gel formation
G4	.5	7.1	211.3	93.53	No gel formation
G5	.5	7.2	230.4	96.48	No gel formation
G6	.5	7.1	356.7	90.29	No gel formation
G7	1	7.0	431.9	95.33	Formation of gel
G8	1	6.8	542.1	90.68	Formation of gel
G9	1	7.0	567.3	92.35	Formation of gel
G10	1.5	6.8	593.7	97.56	Formation of gel
G11	1.5	6.6	634.3	99.32	Formation of gel
G12	1.5	6.8	672.8	90.56	Formation of gel

Table 3: 3^2 full factorial design layout

Batch N0.	Variables levels in coded form		Viscosity* (cp)	Drug content* (%)	% Drug release* (Q_{50})	% Drug release*(Q_{80})
	X_1	X_2				
G1	-1	-1	110	99.11	28.08	99.76
G2	-1	0	150	98.21	26.38	96.48
G3	-1	+1	180	97.38	17.67	92.75
G4	0	-1	200	96.58	16.76	66.65
G5	0	0	223	98.62	13.57	63.59
G6	0	+1	252	99.37	15.36	71.75
G7	+1	-1	278	98.65	7.96	42.50
G8	+1	0	320	97.25	7.35	39.32
G9	+1	+1	132	96.98	7.99	43.12

Table 4: Transaction of coded levels in the actual units

Variables level	Low(-1)	Medium(0)	High(+1)
Concentration of sodium alginate (X_1)	.5%	1%	1.5%
Concentration of sodium citrate (X_2)	.125%	.25%	.s5%
All the batches contain 100mg tinidazole, Vicosity measured at 120 rpm and having the same pH 7.0 ± 0.3.			

4. Evaluation

1. Physical appearance and pH

All the readied alginate situated in-situ arrangement of tinidazole were checked for their clearness and the time needed for gel development. The pH was estimated of in situ arrangement of tinidazole utilizing an adjusted advanced pH meter a 37^0C.

2. In vitro gelation study

Tinidazole in situ arrangement (5ml) and fake invigorated gastric liquid (SGF, 100ml) were blended (1:20,v/v) and gelation was seen by visual assessment.

3. Viscosity

The consistency of sodium alginate arrangement either in arrangement or gel made with counterfeit mimicked gastric liquid was resolved with a Brookfield computerized viscometer (Model No. DV PRO). The detailing (100ml) was taken in a measuring utencil and kept up at room temperature. For assurance of consistency was utilized. Viscosities were resolved at various shear rates from 00 to 100 rpm at room temperature.

4. Determination of drug content

The measure of tinidazole in each example was dictated by spectrophotometer. Precisely, 10ml of in-situ gel was estimated and moved to 100ml of volumetric carafe. To this 50-70 ml of 0.1N HCL was added and shaken on mechanical shaker for 15 min, trailed by sonication for 15 min. complete scattering of substance were guaranteed, outwardly and separated utilizing 0.45 layer channel. From this arrangement, 10 ml with 0.1N HCL. Substances of tinidazole were resolved spectrophotometerically.

5. In vitro release studies

The medication discharge contemplates were done in USP XXVI disintegration test contraption USP Type II (Paddle Method). Volume of disintegration media was 900ml. of Hydrochloric corrosive support arrangement of pH 1.2; temperature 37^0C ± 0.2^0C, RPM was 50. 1ml of test was taken out every hour and it was weakened to 10ml with 0.1N HCL at 368nm. Furthermore, 1ml of test was supplanted in disintegration media to keep up sink condition.

6. pH measurement

The pH of the every plan was dictated by utilizing pH meter. The meter was first adjustment utilizing arrangement of pH 4 and pH 7.

7. Gelling time

It was reviewed in three classes based on gelation time constantly period for which the framed gel stay as it is a) gel following couple of moments, b) scattered quickly, c) gelation prompt, stay for 12hr. Gelation quick, stay for more than 12hr.

8. Floating lag time

In this test 10ml of in-situ detailing was added into the 900ml disintegration vessel containing 0.1N HCL at 37^0C. The time that plan took to arise on surface of disintegration medium is alluded as coasting slack time.

9. Floating duration

In this test 10ml of in situ definition was added into the 900 ml disintegration vessel containing 0.1N HCL at 37^0C. The time that detailing took to remain continually drifting on surface of disintegration medium is alluded as span of coasting.

Table 5: Dissolution of tinidazole in-situ gel

Dissolution medium	900 ml of (0.1N HCL,1.2 pH)
Temperature	37^0C +0.2^{0}C
RPM	50
Volume withdrawn	10ml every 1 hr.
λ max	368 nm
Sol. taken	Ten ml sol. (Known drug content)

5. Result and Discussion

5.1 Determination of UV Absorbance Maxima of Tinidazole

The standard stock arrangement was utilized to assurance the λmax of (0.1 N HCL, pH 1.2) was utilized as clear for the investigation. The range was taken between the UV scope of 200-400nm. The most noteworthy pinnacle acquired from the range investigation was taken as λ max for tinidazole that utilized was discovered to be 368 nm.

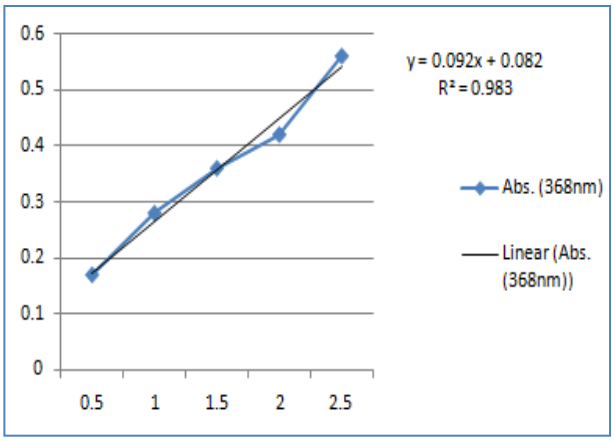

Figure 1: Standard Calibration Curve of Tinidazole

5.2 Recognizable proof of medication by FTIR

ID study was performed utilizing FTIR spectrophotometer. The trademark assimilation pinnacles of Tinidazole were gotten at various wave numbers. The pinnacles got in the spectra of unadulterated medication associate with the pinnacles of authentic range of British Pharmacopeia which affirms the virtue of medication.

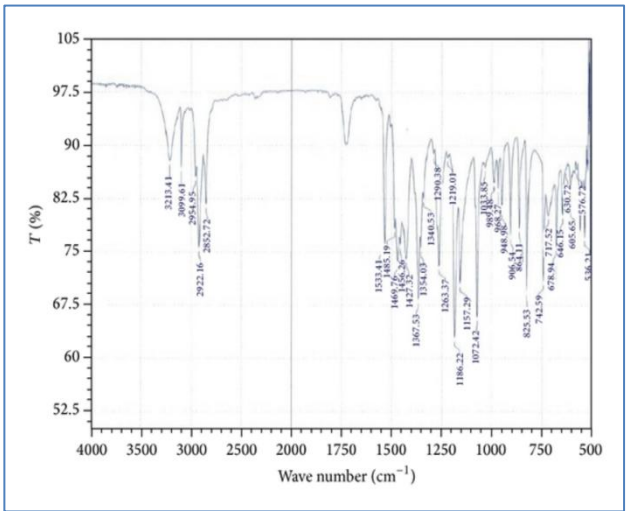

Figure 2: IR spectra of Tinidazole

5.3 Physical Appearance and pH

The prepared sodium alginate based in-situ solution of Tinidazole was checked for their clarity and the type of the solution. After administration of the prepared solution in (0.1N HCL, pH 1.2) also checked the time required for gel formation and type of gel formed.

Table 6: pH of prepared in situ gel formulation

Formulation code	G1	G2	G3	G4	G5	G6	G7	G8	G9
pH	7.4	7.4	7.1	7.3	6.9	7.0	7.4	7.2	6.8

5.4 Viscosity

The viscosity or the formulation increased with an increase in solution alginate concentration. This phenomenon is a consequence of increasing chain interaction with an increase in polymer concentration. Calcium Chloride. Which is the source of cations, increased the viscosity of the formulation. This change in viscosity is due to proportional increase in the amount of dispersed calcium.

Table 7: Viscosity of prepared in situ gel formulation

Formulation code	G1	G2	G3	G4	G5	G6	G7	G8	G9
Viscosity (cp)	110	150	180	200	223	252	278	320	132

5.5 Floating Behaviour

The buoyancy lag time varied with the formulation variables. Formulation F4 exhibited the least buoyancy lag time (41 s) while formulation F2 exihibited the highest lag time (59 s). The decrease in the buoyancy lag time of a can be attributed to the availability of an increased the concentration of calcium carbonate was increased, being entrapped in the formed gel to give rapid buoyancy. Irrespective of formulation variables, buoyancy duration was > 12hours.

Table 8: Floating behaviour of prepared in situ gel formulation

Formulation code	F1	F2	F3	F4	F5	F6	F7	F8	F9
Floating lag time (sec)	50	59	50	40	43	41	46	54	50
Floating time (hr)	>12	>12	>12	>12	>12	>12	>12	>12	>12

5.6 Gelling Capacity

In vitro gelling capacity of various formulation of in-situ is reported in table

Table 9: Gelling capacity of prepared in situ formulation

Formulation code	G1	G2	G3	G4	G5	G6	G7	G8	G9
Gelling capacity	++	++	++	+++	+++	++	+++	+++	+++

5.7**Drug Content**

The medication substance of all (G1-G9) detailing is given in table no.3; it goes in the middle of 99.1% - 96.98%. The qualities are worthy according to United States pharmacopeia principles.

Table 10: Result of drug content of all formulation of Tinidazole

Formulation code	G1	G2	G3	G4	G5	G6	G7	G8	G9
Content uniformity (%)*	99.11	98.21	97.38	96.58	98.62	99.37	98.65	97.25	96.98

5.8In – Vitro Drug Release:

The in-vitro drug arrival of the in-situ gel was conveyed in (0.1N HCL, 1.2pH) arrangement from 0 to 8hrs by utilizing disintegration test device USP Type II (Paddle Method). The example were removed at various time stretches and broke down at 368 nm. Rate Cumulative medication discharge was determined based on mean measure of Tinidazole present in the particular arrangement. The outcome acquired in the in vitro drug discharge for the plan G1 to G9 in (Table 10). Detailing G1,G2,G3,G4,G5,G6,G7,G8 and G9 delivered about 90.03,93.01,86.60,72.59,79.58, 70.16,85.28, 92.

44,84.64 of medication after 8hrs. In this manner, the detailing (93.01) has better outcome as correlation with others plan as sustained delivery.

Table 11: In- vitro Drug of Tinidazole in situ formulation (G1-G9)

Time (Hrs.)	%Cumulative drug release from various batches								
	G1	G2	G3	G4	G5	G6	G7	G8	G9
0	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
1	15.10	23.04	8.09	28.63	21.56	25.45	27.56	23.93	29.78
2	18.03	29.00	21.05	39.00	28.53	33.76	34.41	28.82	36.52
3	45.06	46.76	23.43	42.64	39.46	38.76	41.78	30.11	42.49
4	59.76	62.02	33.45	48.76	44.76	46.56	35.22	50.21	59.62
5	73.56	76.78	38.54	52.56	48.67	50.76	65 32	56.77	61.99
6	86.75	79.65	44.65	57.98	53.56	55.98	71.23	68.43	75.22
7	89.87	88.91	76.54	62.15	68.35	62.64	64.76	71.47	75.20
8	90.03	93.01	86.60	72.59	79.58	70.16	85.28	92.44	84.64

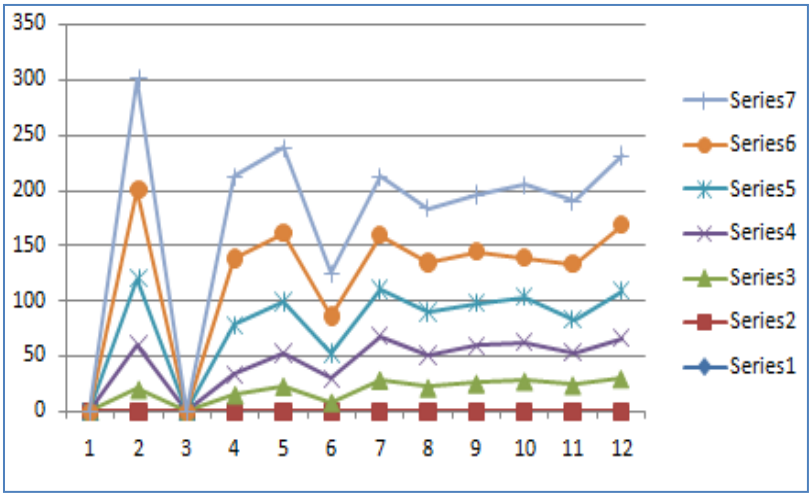

Figure 3: In-vitro Release Profile of Tinidazole (G1-G7)

6. Result & Conclusion:

The present investigation dealt with the formulation, optimization and evaluation of tinidazole in-situ gel. Sodium alginate and sodium citrate used as a polymer and cross-linking agent respectively. The in situ definitions were displayed well, consistency, drug content and continued medication discharge. This investigation reports that oral organization of watery arrangement containing sodium alginate bring about definition of in situ gel. Such plan are homogenous fluid when organization orally and become gel at the contact site. The assessment of the detailing is reliant upon exact outcomes acquired by systematic strategy utilized during the examination. Exact outcomes require the utilization of standard and an adjustment method. Hence, standard plots of Tinidazole were prepared in (0.1N HCL, pH 1.2) solutions. Tinidazole was analysed using UV spectrophotometer. Two different were sodium alginate and sodium citrate used as a polymer and cross- linking agent respectively in the formulation of in situ gel. Among different excipients used calcium chloride. Structure the IR considers it very well might be presumed that the medication and transporters utilized go through actual cooperation these is no substance change, and accordingly the gelling operator, cross-connecting specialist and other excipients are suitable for formulation of in situ gel of tinidazole formulation G1, G2,G3,G4,G5,G6,G7,G8, and G9 released about90.03,93.01,86.60,72.59,79.58,70.16,85.28, 92.44, and 84.64 of drug after 8 hrs

respectively. Indicate that the formulation, G2 which was prepared by the Sodium alginate (1gm) with Tinidazole showed minimum drug release (Sustained drug release, Prolong duration of drug) after 8 hrs. Thus, the formulation (G2) has better result as comparison to other formulations. Consistency and medication arrival of the in situ gel. All other parameter was also observed to be comparable. It very well may be finished up from study that improved definition was steady at room temperature.

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