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Development of Stomach Specific Floating Oral Insitu Gel of Domperidone for Children

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A B S T R A C T

Domperidone, is an antiemetic drug, has been used as an add-on treatment in adults and children. To reduce the dosing frequency of Domperidone especially in case of children, here we made an attempt to develop gastro retentive floating insitu gel formulation. With this effort drug release can be extended upto 12hrs, thereby improving the patient's compliance. Oral insitu gels are in sol form before administration into the body, but once administered, undergo gelation in-situ to form a gel. Six formulations were prepared by ion crosslinking method with varying concentrations of sodium alginate and $CaCO_3$. In the present study, polymers like sodium alginate was usedas a gelling agent and HPMC K15M as a release retardant polymer and $CaCO_3$ was used as a cross-linking agent. Polymers were selected based on drug-polymer compatibility studies by FTIR. All six formulations were subjected to various evaluation parameters like clarity, determination of pH, drug content, viscosity, invitro gelling capacity, buoyancy studies, swelling studies and invitro dug release studies. Among all formulations, F-3 was found to exhibit better floating behaviour and drug release upto 12 hrs. Hence it may be concluded that floating oral insitu gels will be a promising approach to reduce the dosing frequency of paediatric drugs which shows good solubility at acidic pH.

Keywords: Domperidone, Floating insitu gels, HPMC, Ion cross-linking, Sodium alginate.

A R T I C L E I N F O

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1. Introduction

Recent development in technology has provided viable dosage alternatives that can be administered via different routes of administration. Various routes that are used include oral, topical, nasal, rectal, vaginal, ocular etc. But out of these routes oral route of drug delivery is considered as the most favoured and practiced way of delivery due to ease of administration, ease of production and low cost. In case of drugs which either absorb or show local effect within stomach and upper part of intestine should spend maximum time in stomach.This however, is found very difficult to occur; in case of conventional dosage forms [1]. So in order to prolong gastric residence time and to target site specific drug release in the upper GIT for local and systemic effects Gastro Retentive Drug Delivery Systems (GRDDS) are used. GRDDS are oral controlled release formulations can remain in gastric regions for prolonged period of time and significantly increases the Gastric Retention Time (GRT) of drugs. Floating insitu gelis a type of this system which arein sol form before administration but undergo gelation when come in contact with body fluids. Various triggers to induce gelation include pH, ions and temperature [2]. Floating insitu gels or raft forming systems forms a continuous layer called raft which floats on gastric fluids thereby preventing the reflux of the gastric contents (i.e. gastric acid) into the esophagus.

Domperidone is rapidly absorbed from the stomach and upper part of the gastrointestinal tract after the oral administration. It is a weak base with good solubility in acidic pH but in alkaline pH solubility is significantly reduced where the poorly-soluble freebase may be precipitated within the formulation in the intestinal fluid. Precipitated drug is no longer capable of being released from formulation [3]. The bioavailability of Domperidone is about 15% only and the short biological half-life of drug (7 h) also favors development of a sustained release formulation. Hence the low bioavailability and good solubility in acidic pH following oraladministration favours development of a gastro retentive formulations of Domperidone [4]. Domperidone floating insitu gel offers several advantages like easy to manufactureand swallow, reduced dosing frequency, improved bioavailability and patient compliance.

2. Materials and Methods

Materials

Domperidone was obtained as gift sample from Hetero Pharma limited, Hyderabad. All other polymers and chemicals were of either pharmaceutical or analytical grade.

Methods

Drug Excipient Compatibility Study

Drug excipient interactions has been estimated by using FT-IR.

Preparation of Domperidone floating insitu gel

Insitu gels were prepared by ion-activation/ion cross linking method. In this method, we used Sodium alginate as gelling agent, which gels on contact with the divalent cations like Ca^{2+} and monovalent cations like Na^{+}. Hydroxy Propyl Methyl Cellulose (HPMC K15M) as a release retardant polymer and $CaCO_3$ as a cross-linking agent and also acts as a source of Ca++ ions in the solution itself. Due to the free calcium ions being complexed with sodium citrate, gelation was delayed until the administered solution reached the acidic environment of the stomach. Gelation was then occurred as the complex broke down and the Ca++ ions were released [5]. The calcium carbonate present in the gelling formulation released carbon dioxide in gastric environment thereby making the formulation porous and buoyant and prolonging the residence time. Six formulations were prepared with varying concentrations of sodium alginate and $CaCO_3$as shown in Table No.1.

First of all, active material (Domperidone) was passed from sieve # 60 while other inactive ingredients were passed from sieve # 40. In around 30ml deionized water, HPMC was dissolved. Then calcium carbonate and Domperidone (10 mg) was added to it while stirring so that therewas proper and homogenous dispersion of the activematerial in the solution. Again 30mlof deionized water in otherbeaker was heated to NMT 60°C on hot plate anddissolved sodium alginate in it. Cool it to 40°C and to this solution HPMC solution was added or vice-versa. Final solution was sonicated well and final volume was adjusted to 100ml with deionized water [6].

Evaluation of Floating Insitu Gels

Physical appearance and pH measurement

All the formulations were visually checked for their appearance and color. pH was measured in each of the solution using calibrated digital pH meter at 25°C [6].

Determination of drug content

Accurately, 10 ml of in situgel from different batches (equivalent to 1 mg of Domperidone) weremeasured and transferred to 100 ml of volumetric flask.To this 50-70 ml of 0.1 N HCl was added and sonicatedfor 30 min. Volume was adjusted to 100 ml. Completedispersion of contents were ensured, visually andfiltered using Whatman Filter Paper. From this solution, 10 ml of sample was withdrawn and diluted to 100 ml with 0.1 N HCl. Content of Domperidone was determined spectrophotometrically at 284 nm usingdouble beam UV-Visible spectrophotometer [7].

In-vitro gelling capacity

In vitrogelling capacity of prepared formulations was measured by placing 5ml of the gelation solution (0.1N HCl, pH 1.2) in a 15 ml borosilicate glass test tubeand maintained at 37±1ºC temperature. One ml of each formulation was added with the help ofpipette. The formulation was transferred in such a way that places the pipette at surface of fluid in test tube andformulation was slowly released from the pipette. As thesolution comes in contact with gelation solution, it wasimmediately converted into stiff gel like structure. Thegelling capacity of solution was evaluated on the basis ofstiffness of formed gel and time period for which theformed gel remains as such.In-vitrogellingcapacity was graded in three categories on the basis ofgelation time and time period for which the formed gelremains [8]

(+) Gels after few minutes, dispersed rapidly
(++) Gelation immediate remains for 12 hours
(+++) Gelation immediate remains for more than 12hours

***In-vitro* floating ability (In-vitro buoyancy)**

In-vitrofloating study was carried out using900 ml of 0.1N HCl, (pH 1.2) .The medium temperaturewas kept at 37^{o}C. 10ml formulation wasintroduced into the dissolution vessel containing mediumwithout much disturbance. The time the formulation tookto emerge on the medium surface (floating lag time) andthe time the formulation constantly floated on surface ofthe dissolution medium (duration of floating) were noted [9,10].

Viscosity measurement of the in-situ gelling solution

Viscosity of the sols was determined using aBrookfield digital viscometer (DV-E Viscometer) with the spindle number 1. Temperature of the 2 ml aliquot of the sample was kept at 27 ±1ºC during each measurement which lasts 30 sec [11, 12, 13].

Measurement of water uptake by the gel (Swelling studies):

A gel of 100mg was weighed accurately (W_1). It was kept in a petridishand 50ml of 0.1 N HCl was added. The petridish was kept aside for 24 hrs. The weight of swollen matrix gel (W_2) was measured and swelling index was calculated using following formulae [14].

Swelling Index (SI) = $(W_2\text{-}W_1/W_1) \times 100$

Where,

W_1 = initial weight of gel

W_2 = weight of swollen matrix after 24 hrs

In-vitro drug release study [15]

The release of drug from the formulations was determined using a USP/24 dissolution test apparatus with a paddle stirrer at 50 rpm. This speedwas slow enough to avoid the breaking of gelledformulation and was maintaining the mild agitation conditions believed to exist *in-vivo*. The dissolution medium used was 900 ml of 0.1 N HCl, and temperature was maintained at 37º ± 1^{0}C. A sample (1 ml) of the solutionwas withdrawn from the dissolution apparatus atdifferent time intervals. The samples were filteredthrough Whatsman Filter Paper and drug content was determined spectrophotometricallyat 284 nmusing double beam UV-Visible spectrophotometer.

Analysis of the drug release kinetics [16]

The in- vitro drug release data were analyzed by fitting them into different kinetic models in order to investigate the release mechanism of Domperidone from the gel systems. The cumulative amount of drug released from the systems at different time intervals was fitted to different kinetic model of Zero order, First order, Higuchi model and Korsmeyer-Peppas model to find out whether the drug release from the systems provides a constant drug release pattern. The correlation coefficient (R^2) and Release constant were calculated to find the fitness of the data to different kinetic models.

Zero-order model [17]

Drug dissolution from dosage forms that do not disaggregate and release the drug slowly can be represented by the equation:

$$\mathbf{Q_t = Q_0 + K_0 t}$$

Where,

Q_t is the amount of drug dissolved in time t,Q_0 is the initial amount of drug in the solution (most times, $Q_0 = 0$) and K_0 is the zero order release constant expressed in units of concentration/time. Application: This relationship can be used todescribe the drug dissolution of several types ofmodified release pharmaceutical dosage forms, as inthe case of some transdermal systems, as well asmatrix tablets with low soluble drugs in coatedforms, osmotic systems, etc.

First order model [18]

This model has also been used to describeabsorption and/or elimination of drugs. The release of the drugwhich followed first order kinetics can be expressedby the equation:

$$\mathbf{Log\ C = log\ C_0 - K_t / 2.303}$$

Where,

C_0 is the initial concentration of drug, k is thefirst order rate constant, and t is the time. Thedata obtained are plotted as log cumulative percentageof drug remaining *vs*. time which would yield a straight line with a slope of -K/2.303.

Application:

This relationship can be used todescribe the drug dissolution in pharmaceuticaldosage forms such as those containing water-solubledrugs in porous matrices.

Higuchi model [19]

It is used to describe drug release from a matrix system and was proposed by Huguchi. This model is based on the hypotheses that (i) initialdrug concentration in the matrix is much higher thandrug solubility; (ii) drug diffusion takes place onlyin one dimension (edge effect must be negligible);(iii) drug particles are much smaller than systemthickness; (iv) matrix swelling and dissolution arenegligible; (v) drug diffusivity is constant; and (vi)perfect sink conditions are always attained in therelease environment. In a general way the Higuchi modelwas simplified as

$$\mathbf{f_t = Q = K_H \times t^{1/2}}$$

Where,

K_H is the Higuchi dissolution constant. The data obtained were plotted as cumulative percentagedrug release versus square root of time.

Application: This relationship can be used todescribe the drug dissolution from several types ofmodified release pharmaceutical dosage forms, as inthe case of some transdermal systems and matrixtablets with water soluble drugs.

Korsmeyer-Peppas model [20,21]

Korsmeyer derived a simple relationshipwhich described drug release from a polymeric system.To find out the mechanism of drug release, first60% drug release data were fitted in Korsmeyer Peppas model.

$$\mathbf{M_t / M_\infty = Kt^n}$$

Where,

M_t / M_∞ is a fraction of drug released at timet,

k is the release rate constant and n is the releaseexponent.

The n value is used to characterize differentrelease for cylindrical shaped matrices.In this model, the value of *n* characterizes therelease mechanism of drug. For the case of cylindrical tablets, 0.45≥n correspondsto a Fickian diffusion mechanism, 0.45 < n <0.89 to non-Fickian transport, n =

0.89 to Case II (relaxational) transport, and n > 0.89 to super case II transport. To study the release kinetics, data obtained from *in-vitro* drug release studies were plotted as log cumulative percentage drug release versus log time.

3. Results and discussions

Drug –Polymer Compatibility Studies by FTIR

From the observations of FTIR peaks it was concluded that all the polymers used in the formulation were compatible with drug and also with each other.

Formulation development

Total six formulations were prepared with varying concentrations of sodium alginate and $CaCO_3$ by ion cross linking method. All formulations exhibit good gelling capacity, floating behavior, viscosity and invitro drug release.

Evaluation of Floating Insitu Gels

Physical appearance and pH measurement

All the formulations were found to be milky white colored solution. pH measurement is very important for oral preparation otherwise it leads to irritation to the throat. pH was found to be in the acceptable range of 6.8–7.5.pH values of all formulations were shown in Table No.2.

Determination of drug content

Drug content of six formulations were determined and allwere found to have drug content in the range of 96 to 102%, indicating homogenous distribution of drug throughout gel. Table No.2 shows the drug content of the different formulations.

In-vitro gelling capacity

The time for formulation to come to the medium surface (floating lag time/ *In-vitro* gelling capacity) varied with the formulation variables. The *in situ* gel should maintain its integrity without dissolving or eroding for prolonged periods to facilitate controlled release of drugs locally. From the results, it was observed that, with increase in the concentration of $CaCO_3$, floating lag time decreases. Increase in polymer concentration results in an increase in viscosity. Hence time taken by the sol to form a cohesive gel mass and to emerge on the surface of the medium was lowered. Results were shown in Table No.2.

***In-vitro* buoyancy**:

Increasing amounts of Ca^{+2} and CO_2 resulted from the increase in calcium carbonate concentration, are responsible for the observed reduction in floating lag time and increasing duration of floating. All six formulations showed good *in-vitro* buoyancy for more than 12hrs as shown in Table No.2.

Viscosity measurement of the in-situ gelling solution

Rheological properties of prepared solutions were important for oral administration for easy spreadability and pourability. Rheological properties of all formulations illustrated that increase in viscosity with increasing concentration of sodium alginate and calcium carbonate and also due to the presence of HPMC K15M as shown in Table No.3.but these were easily pourable from the container. It was found to be in the range of 33.69 – 84.63 Cps.

Measurement of water uptake by the gel (swelling studies)

Release of the drug from the polymer matrixdepends on the amount of water associated with thesystem. The release of the drug may involve the penetration of water into the matrix and simultaneously release of the drug via diffusion or dissolution. Water uptake by gel was directly proportional to the polymer concentration. As the concentration of the gelling polymers was increased the water uptake by the gel also increased as shown in Table No.3.

***In-vitro* drug release study**

The dissolution profile from all the batches revealed that concentrations of sodium alginate, calcium carbonate and HPMC K15M have an important role in drug release pattern.A significant decrease in rate and extent of drug release was observed with the increase in polymer concentration, and is attributed to increase in the density of the polymer matrix and also increase in the diffusional path length which the drug molecules have to traverse. But sodium alginate alone was not sufficient to produce the drug relapse.

In this study HPMC was added to all formulations to further sustain release of drug,HPMC act as a release retardant and as viscosity enhancing agent.As the percentage of calcium carbonate increased, the release rate decreased due to the stronger gel formation occurred. From the results it was observed that the release of the drug from these gels are characterized by an initial phase of high release (burst effect) followed by a slower release as the gelation proceeds. The dissolution drug release profile was plotted as cumulative % drug release v/s time curve as shown in Figure No.1 and Cumulative Percentage Drug Release of all formulations were shown in Table No.4.

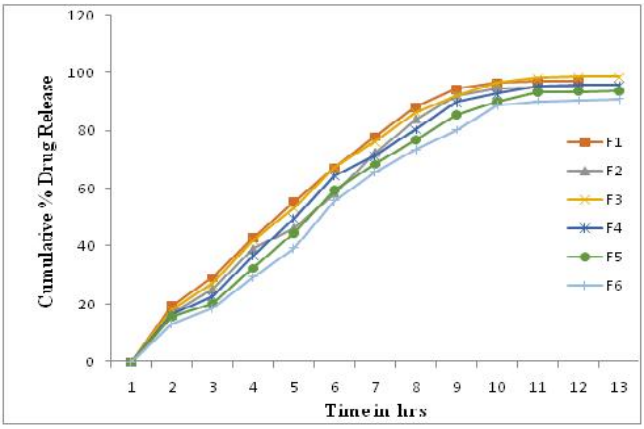

Figure 1: Cumulative Percentage Drug Release of All Formulations

Analysis of the drug release kinetics

The dissolution data so obtained was fitted to various kinetic models like Zero Order, First order, Higuchi and Korsmeyer-Peppas models. Results were shown in Table No.5. The release of drug from the in-situ gel followed zero and Higuchi model and the release process was found to occur by an non fickian diffusion-controlled mechanism as n value obtained for the best fit model was above 0.45 and below 0.85.

Table 1: Composition of floating in situ gels of Domperidone

Formulation code	F1	F2	F3	F4	F5	F6
Domperidone	100mg	100mg	100mg	100mg	100mg	100mg
Sodium alginate	1g	1g	1.5g	1.5g	2g	2g
Sodium citrate	5000mg	500mg	500mg	500mg	500mg	500mg
Calcium carbonate	250mg	500mg	250mg	500mg	250mg	500mg
HPMC K15M	600mg	600mg	600mg	600mg	600mg	600mg
Deionized water	Up to100ml	Up to100ml	Up to100ml	Up to100ml	Up to100ml	Up to100ml

Table 2: Evaluation tests of Domperidone floating insitu gels

Formulation Code	Ph	Drug content (%)	Gelling Study	Floating lag time (sec)	Duration of floating (hr)
F1	7.0	96.59	++	25	>12
F2	6.9	97.56	+++	20	>12
F3	6.8	99.80	+++	15	>12
F4	7.3	97.45	++	9	>12
F5	7.0	100.20	++	5	>12
F6	7.5	101.60	+++	2	>12

Table 3: Viscosity and swelling index of Domperidoneinsitu gels

Formulation Code	Viscosity (Cps)	Swelling index (%)
F1	130.2	40.28
F2	192.4	33.69
F3	210.9	60.32
F4	260.8	48.79
F5	273.6	84.63
F6	292.5	71.23

Table 4: Cumulative Percentage Drug Release of all Formulations

Time in hrs	Cumulative percentage drug release					
	F1	**F2**	**F3**	**F4**	**F5**	**F6**
0	0	0	0	0	0	0
1	19.4	17.03	18.22	16.33	15.64	13.24
2	29.2	25.21	27.08	22.57	20.23	18.69
3	43.07	39.06	42.06	36.84	32.47	29.46
4	55.37	46.31	53.23	49.63	44.62	39.27
5	67.05	58.3	67.19	64.42	59.66	55.79
6	78.08	72.39	76.09	71.23	68.45	65.76
7	88.22	83.94	86.36	80.46	76.77	73.39
8	94.41	92.14	92.14	89.95	85.51	80.26
9	96.53	94.66	96.54	92.65	90.23	88.64
10	96.9	94.89	98.14	95.42	93.44	90.24
11	96.9	94.89	**98.54**	95.68	93.63	90.45
12	-	-	**98.54**	95.68	93.88	90.89

Table 5: Mechanism of drug release of all formulations

Formulation code	Correlation coefficient values (R^2)			Diffusion exponent value (n) in Peppa's model
	Zero order	**First order**	**Higuchi's model**	
F1	0.99582	0.93649	0.97143	0.68879
F2	0.99634	0.91693	0.99372	0.79340
F3	0.99806	0.94263	0.99463	0.75892
F4	0.99184	0.92334	0.98932	0.78203
F5	0.99677	0.91269	0.99643	0.64823
F6	0.99723	0.90645	0.99421	0.81487

4. Conclusion

Domperidone, a dopamine D_2 receptor antagonist, is used as a prokinetic and antiemetic agent for the treatment of gastroparesis, nausea and vomiting.In the present work we made an attempt to develop stomach specific floating oral insitu gel of Domperidone, which increases the gastric residence time, ease of administration, reduced dosing frequency and thereby improving the bioavailability of the drug. All Domperidone floating insitu gel formulations showed good *in-vitro* buoyancy and *in-vitro* drug release out of which F3 showed best results by sustaining its drug release upto 12hrs. Hence we concluded that this formulation is especially advantageous for children because of reduced dosing frequency and improved patient's compliance and further work is recommended to support its efficacy claims by *in-vivo* studies.

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