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DEVELOPMENT AND MICROMERITIC EVALUATION OF FLOATING GRANULES OF CINNARIZINE

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ABSTRACT

The objective of study was to design and optimized a controlled release system of cinnarizine to increase its bioavailability by increasing the residence time in the stomach without contact with the mucosa and was achieved through the preparation of floating granules by melt granulation and melt solidification techniques. Cinnarizine, a H_1-receptor antagonist, prescribed medication for the treatment for vestibular vertigo disorders and motion sickness was chosen as the drug candidate to be formulated as gastro retentive multiparticulate system as it is a weekly basic drug with a short half life of 5 hrs, showing gastric pH dependent bioavailability. Gelucire 43/01 was selected as a lipid carrier in different ratio (1:0.5, 1:1, 1:1.5) along with drug. The formulation F1 to F9 were prepared and evaluated for dependent variable (in vitro floating ability) and formulation F4 to F9 were evaluated for micromeritic properties, drug content and percentage yield, in-vitro drug release, percentage in-vitro floating ability and formulation F5 was selected as optimized formulation that exhibited good floating ability. In conclusion, hydrophobic lipid, Gelucire 43/01 can be considered as an effective carrier for design of a multiple unit floating drug delivery system of cinnarizine.

KEYWORDS: Cinnarizine; Bioavailability; Floating; Hydrophobic.

INTRODUCTION

One requisite for successful performance of oral controlled release drug delivery system is that drug should have good absorption throughout the GIT, preferably by passive diffusion. Oral controlled release dosage forms are not suitable for variety of Important drugs characterized by a narrow absorption window in the upper part of the GIT (stomach and small intestine). This is due to the relatively short transit time of the dosage form in these anatomical segments. Thus after, only a short period of less than 6 hrs, the controlled release dosage form has already left the upper GIT and the drug is released in short non absorbing distal segment of GIT. This results in the short absorption phase, which is then accompanied by lesser bioavailability. Prolonged gastric retention of drug delivery system in certain situation may be desirable to improve the bioavailability and the therapeutic efficacy of the drugs. After oral administration, dosage form would be retained in stomach and will release the drug in a controlled and prolonged manner, so that drug could be supplied continuously to its absorption sites in the upper part of GIT.

Importance of the dosage form with prolonged residence time in the stomach for,

- Drugs that is locally active in the stomach eg. Drugs used in the education of helicobacter pylori, eg. Tetracycline[1]
- Drugs that is unsuitable in the intestinal or colonic environment eg. Ranitidine.[2]
- Drug having low solubility at high pH values e.g. Verapamil[3]

GASTROINTESTINAL PHYSIOLOGY

GASTRIC pH

Fasting gastric ph is usually steady and approximates 2, but there are short periods of 7-6 minutes characterized by higher pH values. Food buffers neutralize gastric acid, thus increasing the pH up to about 6.5. After meal ingestion is completed, the pH rapidly falls back below 5 and then gradually declines to fasting state values over a period of few hours.[4]

GASTRIC DYNAMICS

It is recognized that the GIT is always in a state of continuous motility. There are two modes of motility pattern: the digestive mode and the interdigestive mode, both involved in the digestion of food. As a result, the biological activity of the orally administered drugs may be different depending upon the state of feeding.[5]

Fasted state is associated with various cyclic events regulating the GI motility patterns, commonly called as the migrating motor complex (MMC). The MMC is organized into alternative cycle of activity and quiescence and can be subdivided into basal, preburst and burst intervals (phase I, II and III respectively).

PHASE I
The quiescent period lasts from 30-60 min and is characterized by lack of any secretary, electrical and contractile motions.

PHASE II
It exhibits intermittent action potential for 20-40 min with increase in contractile motions.

PHASE III
It shows the prevalence of intense large and regular contractions that sweep off the undigested food. These are also called "house keeper waves" and propagate for 10-20 min.

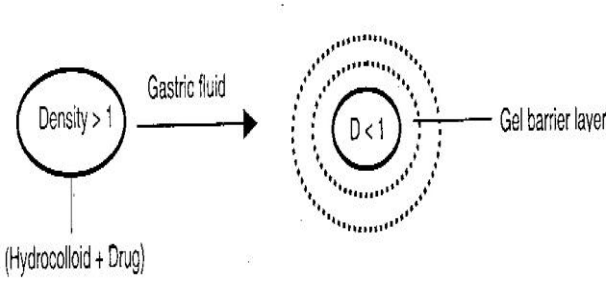
PHASE IV
It is the transition period of 0-5 min between phase III and phase I. These interdigestive series of electrical events originates in the foregut and propagate to terminal ileum in fasted state and repeat cyclically every 2-3 hours. Feeding results in the origination of a continuous pattern of spike potentials and contractions called the postprandial motility.[6]

Floating drug delivery systems (FDDS) are the drug delivery systems having a bulk density lower than the gastric content and they remain buoyant in the stomach for a prolonged period of time, with the potential for continuous release of drug. Eventually, the residual system is emptied from the stomach. Gastric emptying is much more rapid in the fasting state and the floating system relies heavily on the presence of food to retard emptying.

BROAD CLASSIFICATION OF FDDS

1. NON EFFERVESCENT FDDS

The non-effervescent FDDS use gel forming or highly swellable cellulose type hydrocolloids, polysaccharides or matrix forming polymers like polyacrylate, polycarbonate, polystyrene and polymethacrylate. The FDDS is formulated by thorough mixing of the drug and the gel forming colloid. After oral administration, this dosage form swells in contact with gastric fluid, attains a bulk density of < 1, and the air entrapped within the swollen matrix imparts buoyancy to the dosage form, thus floats.[7]



SWELLING OF COLLOIDAL G
Fig 1- swelling behavior of colloidal gel

2. EFFERVESCENT FDDS

These floating delivery systems employ matrices from swelling polymer like methocel® or Chitosan and effervescent components such as sodium bicarbonate and tartaric or citric acid or matrices having chambers of liquids components that gasifies at body temperature. When they come in contact with stomach fluid, CO_2 is generated, and retained entrapped in the hydrocolloid gel, which leads to an upward drift of the dosage form and maintains it in floating conditions.

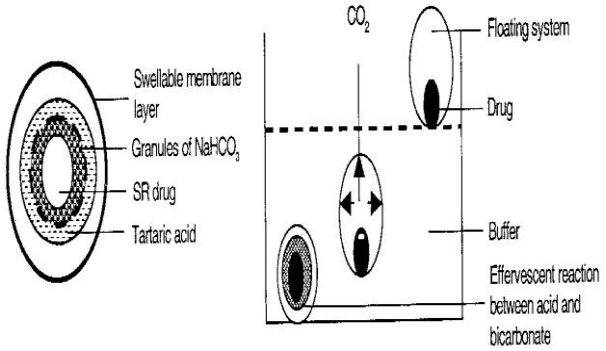


Fig 2- floating of multiple-unit FDDS by liberation of Co_2

ADVANTAGES ASSOCIATED WITH FDDS

- Slow release of drug at a desired rate from the system.
- Expulsion of the floating system from stomach after complete release of drug
- Reduction in dosing frequency
- Increase in gastric retention time (GRT)
- Increased patient compliance
- Reduction in fluctuations in plasma drug concentration.
- Controlled administration of the therapeutic dose at a desirable delivery rate.

MATERIAL AND METHODS

Materials

Cinnarizine (Glenmark pharmaceuticals, baddi); Gelucire 43/01 & Gelucire 50/13 (Gattefosse, St Priest, Cedex, France); Acetone , Potassium chloride, Hydrochloric acid, Potassium dihydrogen phosphate, Sodium hydroxide pellets & Ethanol (Qualigens Fine chemicals, Mumbai); Sodium lauryl sulphate and N-N Dimethyl

formamide (Qualigens Fine chemicals Pvt. Ltd., New Delhi) were purchase from the sources indicated.

PREPARATION OF GRANULES OF CINNARIZINE

The granules of cinnarizine were prepared by using the following methods.

1. MELT GRANULATION METHOD

Lipid was melted at 50-60^{o}C and the drug was added, mixed well, and cooled to room temperature. The mass was passed through a 710um (22 mesh) sieve to obtain uniform sized granules.

2. MELT SOLIDIFICATION METHOD

The drug and lipid polymer were melted on a water bath maintained at 100-110^{o}C, stirred it for uniform molten mass, and cooled at 5^{o}C using ice. The mass was passed out through a 710 um (22 mesh) sieve to obtain uniform sized granules. The formulation codes of the granules prepared are listed in below table.

Table 1- formulation design of cinnarizine granules

Method of preparation	Formulation code	Drug (cinnarizine)	Gelucire 50/13	Gelucire 43/01
Melt granulation method	F_1	1	0.5	-
	F_2	1	1	-
	F_3	1	1.5	-
	F_4	1	-	0.5
	F_5	1	-	1
	F_6	1	-	1.5
Melt solidification method	F_7	1	-	0.5
	F_8	1	-	1
	F_9	1	-	1.5

EVALUATION

1. DETERMINATION OF FLOATING BEHAVIOUR

Twenty unit granules were placed in 900 ml of distilled water and simulated gastric fluid (pH 1.2 buffers) in a vessel maintained at 37^{0}C and stirred at 100 rpm in USP 24 type IInd dissolution test apparatus. The percentage of floating granules up to 8 hours was determined and the floating times were measured by visual observation.

2. DETERMINATION OF BULK AND TAPPED DENSITY

2mg of different optimized formulation was subjected into 10ml graduated measuring cylinder separately and the volume was noted down. The graduated cylinder was tapped 50 times using bulk density apparatus. The bulk density and tapped density was determined using following formula.

Bulk density = weight of floating granules/ initial volume

Tapped density = weighed of floating granules / final volume after tapping

3. DETERMINATION OF GRANULE DENSITY

Granule density of different formulation was determined by liquid displacement method by suspending the granules in a solvent in which the granules were insoluble like liquid paraffin.

4. DETERMINATION OF HAUSNER'S RATIO

The density determinations were used to determine the Hausner's ratio and could be determined using following formula.

Hausner's ratio = Tapped density / Bulk density

5. DETERMINATION OF CARR'S COMPRESSIBILITY INDEX

The density determinations were used to determine the Carr's compressibility index and could be determined by following formula.

$$\textbf{Carr's compressibility index} = \frac{\textbf{Tapped density} - \textbf{fluff density}}{\textbf{Tapped density}} \times 100$$

6. DETERMINATION OF ANGLE OF REPOSE

The angle of repose of different formulation was determined by fixed funnel method and could be determined by using following formula.

Angle of repose = $\tan^{-1}$ (h / r)

Where,

h and **r** are height of pile and radius of the base of the pile respectively.

7. DETERMINATION OF DRUG CONTENT AND PERCENTAGE YIELD

10 mg of floating granules were added to 10 ml of pH 1.2 (0.1 N HCl), heated to 60^{o}C to 70^{o}C, and allowed to cool to room temperature. The lipid was solidified and the drug solution was filtered through whatman no. 1 paper (Whatman plc, Middlesex, UK). The sample was analyzed for drug content by UV spectrophotometer at 254 nm after suitable dilution. Determinations were performed in triplicate. Percentage yield of each formulation was calculated.

8. DETERMINATION OF *IN-VITRO* FLOATING ABILITY

20 unit granules were placed in 900ml of simulated gastric fluid (pH 1.2 buffers) and phosphate buffers pH

2.5, 4.5 & 6.5 in a vessel maintained at 37°C and stirred at 100 rpm in USP 24 type II dissolution test apparatus. The percentage of floating granules up to 8 hours was determined and the floating times were measured by visual observation.

% of floating ability = $[N_f / (N_f + N_s)]$ 100

Where, N_f and N_s are numbers of the floating and settled granules respectively.

RESULT AND DISCUSSION

1. DETERMINATION OF FLOATING BEHAVIOUR

Formulations F_1 to F_2 were prepared and evaluated for dependant variable like percentage floating ability formulations F_4, F_5, F_6, F_7, F_8, & F_9 were selected as optimised formulations as it exhibited good floating ability. Formulations F_1, F_2 & F_3 were rejected based on low value of percentage floating ability.

Table 2: Observation table of in-vitro floating ability in distilled water and pH 1.2 buffer

Formulation code	In-vitro floating ability	
	Distilled water	pH 1.2 buffer
F_1	Sink (with in 1 hour)	Sink (with in 1 hour)
F_2	Sink (with in 1 hour)	Sink (with in 1 hour)
F_3	Sink (with in 1 hour)	Sink (with in 1 hour)
F_4	Float (8 hours)	Float (8 hours)
F_5	Float (8 hours)	Float (8 hours)
F_6	Float (8 hours)	Float (8 hours)
F_7	Float (8 hours)	Float (8 hours)
F_8	Float (8 hours)	Float (8 hours)
F_9	Float (8 hours)	Float (8 hours)

2. DETRMINATION OF BULK DENSITY AND TAPPED DENSITY

The bulk density and tapped density was determined using bulk density apparatus and represented in following table. The bulk density and tapped density of priliminary optimized formulations (F_4-F_9) were found to be in the range of 0.244-0.268 g/cm^3 and 0.304-0.345 g/cm^3.

3. DETERMINATION OF GRANULE DENSITY

The granule density, measured by liquid displacement method by suspending the granules in a solvent I which the granules were insoluble like liquid paraffin, ranged from 0.659-0.760 g/cm3, which is less than 1.004 g/cm3,[8] the specific gravity of the gastric fluid, substantiating the buoyant properties of the granules.

4. DETERMINATION OF HAUSNER'S RATIO

The Hausner's ratio of different formulations were determined and found to be in the range of 0.775-0.821 and indicated good flow property.

5. DETERMINATION OF CARR'S COMPRESSIBILITY INDEX

The Carr's compressibility index of different formulations were determined and found to be in the range if 17.86 – 22.45 % which indicated fair to passable flow property.

6. DETERMINATION OF ANGLE OF REPOSE (θ)

The angle of repose of different formulations were determined and found to be in the range of 14.93-17.52^0 indicated excellent flow property.

Table 3: Micromeritic properties of preliminary optimized formulations

Formulation code	Bulk density±S.D. (g/cm^3)	Tapped density±S.D. (g/cm^3)	Granule density±S.D. (g/cm^3)	Hausner's ratio±S.D.	Carr's compressibil-ity index±S.D.	Angle of repose ± S.D.
F_4	0.258±0.0015	0.324±0.0030	0.713±0.0021	0.796±0.0014	20.42±0.023	16.24^O ±0.015^O
F_5	0.244±0.0021	0.305±0.0026	0.760±0.014	0.801±0.0019	19.86±0.030	14.93^O ±0.029^O
F_6	0.258±0.0020	0.314±0.0028	0.665±0.010	0.821±0.0018	17.86±0.19	17.26^O ±0.040^O
F_7	0.268±0.0021	0.346±0.0025	0.659±0.0029	0.775±0.0015	22.45±0.021	17.42^O ±0.035^O
F_8	0.264±0.0019	0.339±0.0019	0.678±0.0029	0.778±0.0019	22.21±0.019	17.52^O ±0.042^O
F_9	0.260±0.0027	0.326±0.0023	0.686±0.0021	0.799±0.0021	20.15±0.24	16.09^O ±0.036^O

7. DETERMINATION OF DRUG CONTENT AND PERCENTAGE YIELD

The percentage yield and drug content of different formulations were determined and represented in following table. The percentage yield and drug content was found in the range of 89.54- 92.54 and 96.97-98.28%. Low values of standard deviation indicated the uniformity in drug content.

Table 4: Observation table of percentage yield and percentage drug content

Formulation code	Percentage yield	Drug content(%)± S.D
F_4	92.54	98.28±0.545
F_5	90.36	98.17±0.676
F_6	89.36	97.41±0.496
F_7	91.86	97.86±0.705
F_8	90.23	97.66±0.509
F_9	89.54	96.97±0.785

8. DETERMINATION OF *IN-VITRO* FLOATING ABILITY

The percentage *in-vitro* floating ability of different formulations were determined and represented in following table. Formulations F_4-F_9 exhibited 90 to 100 % floating ability at the end of 8 hours in pH 1.2 (0.1 N HCl) buffer and phosphate buffers pH 2.5, 4.5, 6.5. This is due to the lower bulk density of the formulations and hydrophobic nature of Gelucire 43/01 used in granules.

Table 5 : Observation table of percentage in-vitro floating ability in different buffers.

Formuation code	Percentage in-vitro floating ability			
	pH 1.2 buffer	pH 2.5 phosphate buffer	pH 4.5 phosphate buffer	pH 6.5 phosphate buffer
F_4	100	100	95	95
F_5	100	100	95	95
F_6	100	100	95	95
F_7	100	100	100	95
F_8	100	100	95	95
F_9	100	100	95	95

CONCLUSION

The present study was aimed to prepared floating granular delivery system with an objective to control the release rate of cinnarizine. The performance of the formulations was evaluated and the floating ability of the granules and the release rate of the drug (cinnarizine) from the granules can be controlled by changing the composition ratio of Gelucire 43/01. formulation F5 (Drug: Gelucire 43/01 ratio 1:1) show signs of good flow and floating properties, selected as optimized formulation. The study demonstrated that hydrophobic lipid Gelucire 43/01, can be as an effective carrier for the design of a multi unit floating drug delivery system of cinnarizine.

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