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FLOATING DRUG DELIVERY: AN EFFECTIVE TREATMENT FOR DYSMENORRHEA

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ABSTRACT
Dysmenorrhea is a medical term that describes the word ‘‘menstrual pain”, women suffer from primary and secondary dysmenorrhea. Non-steroidal anti-inflammatory medicines such as hormonal drugs are used for the treatment of dysmenorrhea, and diagnostic tests are available for dysmenorrhea such as ultrasonography, laparoscopy, and magnetic resonance imaging (MRI). Non-steroidal anti-inflammatory drugs help in reducing pain and continue to be the first-line treatment recommended for menstrual discomfort. This study evaluated various excipients for their floating behaviour and *in-vitro* profiles of floating tablets. Purpose of floating on this review by reducing contractions of the smooth muscles of the abdomen.
This review focuses on methods for the preparation of floating tablets, the following techniques were reported as direct compression, melt granulation, melt solidification, spray drying, and wet granulation. Pre-compression parameters like angle of repose, bulk density, and tapped density, also evaluation parameters such as drug content, Differential Scanning Calorimetry (DSC), tablet thickness, friability, weight variation, *in-vitro* buoyancy, index swelling, and drug release were reported. This review gives an idea about the polymer which are suitable and compatible with the drug for the preparation of floating tablets and the effect of polymer, gas forming agent.
A review concludes that a floating medicine delivery device is the most effective treatment for dysmenorrhea. everyday activities are delayed by menstrual symptoms associated with dysmenorrhea, such as cramping and stomach ache. The floating drug delivery system is one of the best drug administration methods that can preserve a medication for a long period of time and increase its therapeutic efficacy. The first-line treatment for menstrual pain is still non-steroidal anti-inflammatory drugs. So floating drug delivery can be a better alternative for previously existing treatments and dosage forms.

Keywords: Floating tablet, Dysmenorrhea, Polymer

INTRODUCTION

Dysmenorrhea is medical condition characterised by sever uterine pain during menstruation manifesting as cyclical lower abdominal or pelvic pain, which may also radiate to back and thighs[1]. The word "dysmenorrhea" is derived from the Greek words *dys* means difficult, painful or abnormal *meno* means month and *rrhea* means flow[2]. However, this term is currently used to describe the painful menstruation. Thus, dysmenorrhea refers to an uncomfortable monthly flow[3].

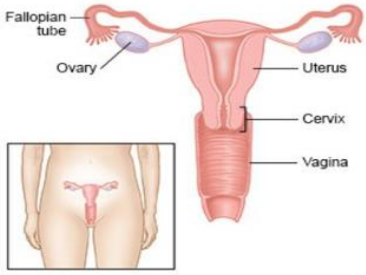

Figure No 1: Female reproductive system

Normal menstrual cramps and dysmenorrhoea vary in that the latter requires medication and makes it impossible to carry out daily activities. The term "dysmenorrhoea" refers to uncomfortable menstrual cramps that have uterine origins [4]. The most frequent reason for pelvic pain and menstrual irregularities in women of childbearing age[5]. One of the most common, uncomfortable gynaecological conditions affecting women's quality of life and social interactions is dysmenorrhea [6]. Primary dysmenorrhea's occurrence and severity may differ depending on a variety of factors, including mental health [7].

The patient recorded her menstrual pain using a 10 cm long visual analogue scale that ranged from 0 ("no pain") to 10 ("very severe pain")[8]. Maximum pain, the highest pain score granted throughout each period, and the sum of the individual daily scores during the time were the two parameters used to study pain [9,10].

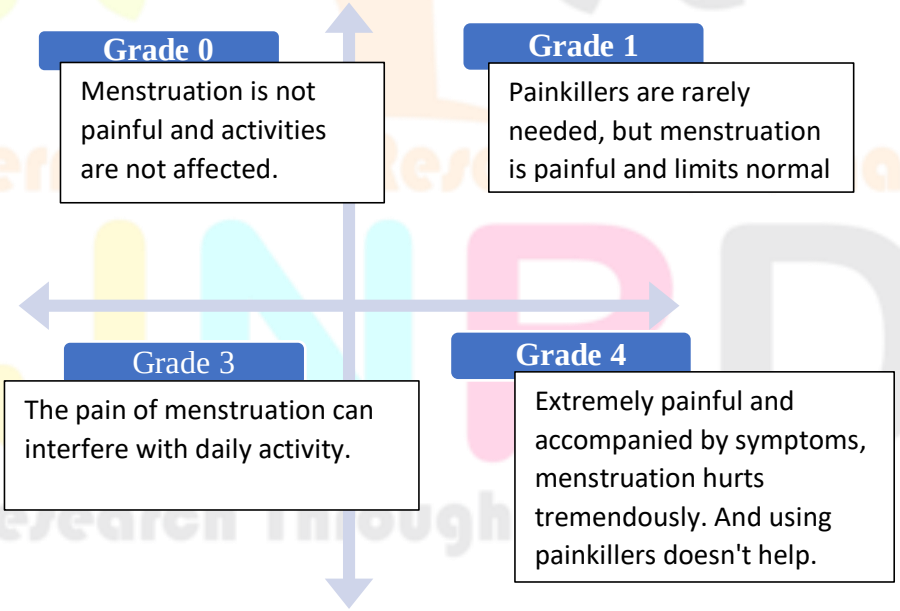

Table No 1: **Dysmenorrhea pain scoring system**

TYPE OF DYSMENORRHEA

Primary dysmenorrhea

The most common gynaecological issue throughout is primary dysmenorrhea, often known as painful menstruation or the absent of any specific pelvic disorders[10]. It is one of the most common complaints of women [11]. When adolescent females go through their first ovulatory cycle, primary dysmenorrhea begins. Its prevalence climbs throughout adolescence (15–17 years), peaks in the 20–24year range, and then gradually reduces after that. Typically, the discomfort associated with this disease begins a few hours before or after the start of menstruation and lasts for 24 to 48 hours [12,13].

Secondary dysmenorrhea

Menstrual pain that is related to an underlying pelvic pathology, such as endometriosis, pelvic inflammatory disease, congenital müllerian defects, or ovarian cysts, is known as secondary dysmenorrhea (SD)[14]. It may not start until many years following menarche. Secondary dysmenorrhea may be influenced by a range of physiological, environmental, and behavioural variables[15,16].

Dysmenorrhea is divided into two kinds, which are shown in the Table 2 [17,18].

Table No 2: Types of dysmenorrhea

Parameters	Primary Dysmenorrhea	Secondary Dysmenorrhea
Onset	Within 3 yr. after menarche	More than 5 yr. after Menarche
Age	15-25 yr. old	Over 30 yr. old
Aging	Gradually improve	Become worse
Postpartum	Improve	No change
Findings of internal Examination	Normal	Endometriosis, fibroids, Adenomyosis
Time	Menstruation	Menstruation or other time if Worse
Duration	4-48 hr	1-5 day

SYMPTOMS

Primary Dysmenorrhea (PD)

- Spasmodic pain usually concentrated in the suprapubic area.
- Pain back of the legs or the lower back.
- Mood changes.
- Fatigue.
- Headache.
- Nausea and edema[19,20].

Secondary Dysmenorrhea (SD)

- More painful.
- Irregular bleeding may occur other than menses.
- Endometriosis.
- Uterine fibroids.
- Depression and stress[21,22].

DIAGNOSIS OF DYSMENORRHEA

Diagnosis of Dysmenorrhea include medical history, physical and pelvic pain examination.

- Ultrasound.
- Laparoscopy.
- Magnetic resonance imaging (MRI)
- Hysteroscopy[23,24].

TREATMENTS FOR DYSMENORRHOEA

Better treatments for dysmenorrhea are shown in figure 2 [25,26,27].

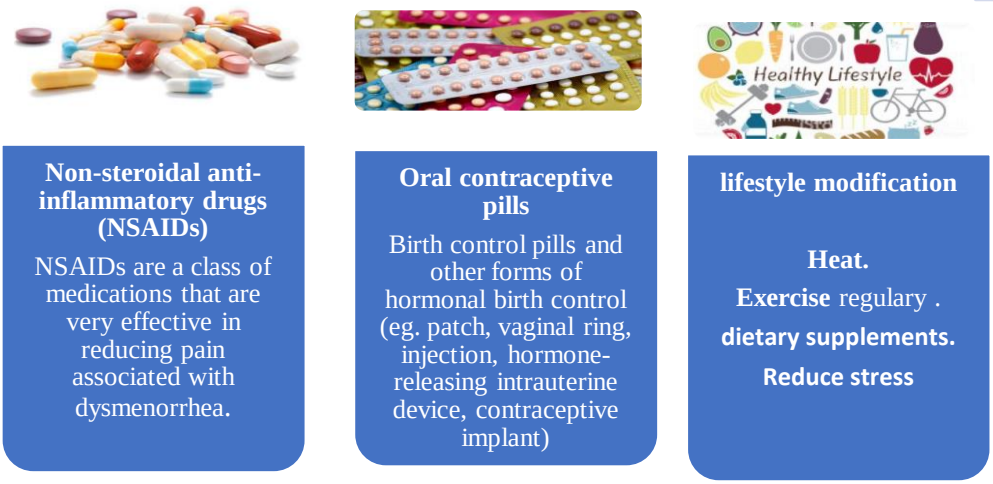

Figure No 2: Treatment of dysmenorrhea

FLOATING DRUG DELIVERY SYSTEM

Gastric retentive dosage forms can monitor how quickly the stomach empties and have a longer half-life in the stomach than conventional dosage forms [28]. To address a number of problems, the extended-release dosage delivery forms improved drug absorption and increased bioavailability[29]. Low-density devices, also referred to as floating drug delivery systems (FDDS), can float over the stomach's contents for a considerable amount of time. Buoyancy may increase retention time and decrease dosing frequency. When a system is effervescent, it produces gas (CO2) that makes it denser and enables it to float inside the stomach[30,31].

STOMACH PHYSIOLOGY

Between the oesophagus and small intestine, there is an extended portion of the digestive tract called the stomach[32]. The stomach's wall is architecturally identical to the walls of the other portions of the digestive tract, but it has an additional, oblique layer of smooth muscle inside the circular layer that helps the stomach perform intricate grinding actions. When the stomach is empty, it contracts, throwing up the mucosa and submucosa into discrete folds known as rugae[33,34].

the four primary secretary epithelial cell types that line the surface of the stomach and descend into the gastric pits and glands are as follows:

• Mucous cells: release alkaline mucus to shield the epithelium from acid and shear stress.
Hydrochloric acid is secreted by parietal cells.
• Chief cells release the proteolytic enzyme pepsin.
• G cells: release the gastrin hormone. Two fundamental purposes are served by the contraction of the stomach smooth muscle:

Gastric emptying is the process by which the ingested food is driven through the pyloric canal and into the small intestine after being crushed, powdered, combined, and liquefied to create Chyme

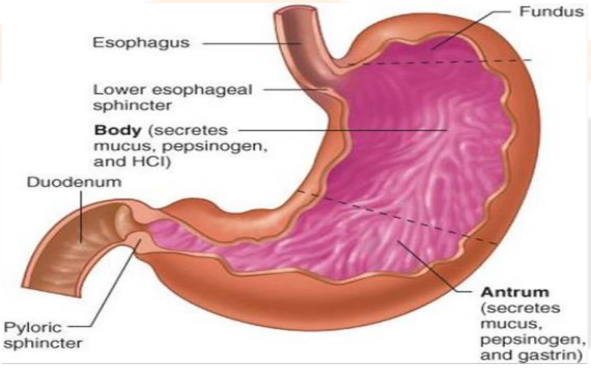

Figure No 3: Structure of stomach

The fundus, body, and antrum are the three physically distinct regions of the stomach (pylorus).
Fundus: the closest component.
Body: serves as a holding area for undigested matter,
Pylorus: By pushing movements, it serves as a place for mixing contents and as a pump for gastric emptying [35,36].

lists the key characteristics of the GI tract [37].

Table No 3: Salient features of GI tract

Segment	Function	pH
Stomach	Digestion of food	1-3.5
Duodenum	Neutralization of acids	4-6.5
Jejunum	Absorption of nutrients	5-7
Ileum	Absorption of nutrients	6-8
Colon	Absorption of water	6-8

CLASSIFICATION OF FLOATING DRUG DELIVERY SYSTEMS

A. **Effervescent FDDS**

1. Gas generating system
2. Volatile liquid containing system

B. **Non-Effervescent FDDS**

1. Colloidal gel barrier system
2. Bi-layer floating tablets
3. Microporous compartment system
4. Floating Beads/ Alginate Beads
5. Micro balloons/ Hollow Microspheres

C. Raft forming system

Effervescent FDDS

Gas generation system

This system uses a floating chamber that is either filled with water, vacuum, air, or inert gas. Due to an effervescent reaction between the organic acid (citric acid) and the carbonate or bicarbonate salts, you can add CO2 to the floating chamber. Such a device utilizes a matrix composed of effervescent materials such as citric acid, sodium bicarbonate, and tartaric acid, swellable polymers such chitosan-like polysaccharides, or chambers filled with a liquid that poses a danger of adverse effects when it is at body temperature[38,39].

Non-Effervescent FDDS

The non-effervescent FDDS in the GI tract works by swelling polymers or by bio adhering to the mucosal layer. The excipients that are most frequently utilized in non-effervescent FDDS are hydrophilic gums and hydrocolloids of the cellulose type that form gels or are highly swellable[40].

Bio adhesive polymers including Carbopol and Chitosan, as well as polysaccharides and matrix-forming substances like polymethacrylate, polycarbonate, polystyrene, and polyacrylate [41].

Colloidal gel barrier systems / Single layer floating tablets

Such systems have a high concentration of one or more hydrocolloids of the cellulose type that produce gels, polysaccharides, and matrix and are very swellable[42].

Bi-layer floating tablets

The immediate release layer of a bi-layer tablet releases the initial dose from the system. The sustained release layer absorbs stomach fluid, forming an impermeable colloidal gel barrier on its surface, and maintaining a bulk density of less than 1[43].

Micro porous compartment systems

This method works by enclosing a drug reservoir inside a tiny compartment that has holes along its top and bottom sides [44].

Floating beads / Alginate beads

Oral dosage forms of multi-particulate drug delivery systems are frequently made up of a variety of tiny discrete units[45].

Micro balloons/Hollow microspheres

Hollow microspheres, commonly referred to as micro balloons, were discovered to float in vitro for 12 hours when submerged in aqueous solution. System for Raft Forming Raft producing systems are frequently taken into consideration for the delivery of antacids and other drugs for gastro-infection and gastro-intestinal illnesses. The gel-forming solution expands when it comes into touch with gastric fluid, generating a viscous compact gel with trapped CO2 bubbles that forms a raft layer on top of gastric fluid and releases the medication material into the stomach over time[46].

Hydrodynamically Balanced System

Drugs with superior acid solubility and those with a specific location of absorption in the upper part of the small intestine are best suited for hydrodynamically balanced systems. The dose form must have a bulk density of

less than 1 in order to stay in the stomach for a long time. It needs to remain in the stomach, preserve its build, and continuously release the medication from the dose form[47].

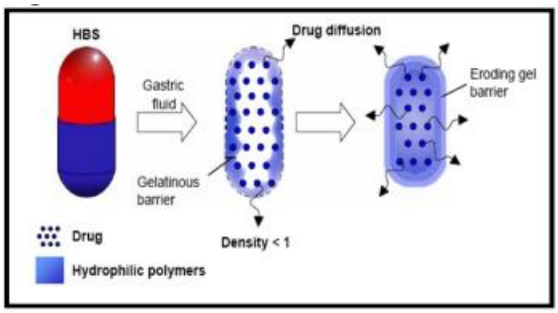

Figure No 4: Hydrodynamically Balanced System

Excipients Added to Various Floating Dosage Forms

• Citric acid, tartaric acid, sodium bicarbonate, Di-SGC (disodium glycine carbonate), and CG are a few examples of effervescent agents.

• Rate of release Retardants: Materials including talc, dicalcium phosphate, and magnesium stearate are utilized to slow the rate of release.

• Inert fatty substances, such as long chain fatty alcohols, beeswax, fatty acids, and gelatin.

• Accelerators of the release rate, such as lactose and mannitol.

• Hydrocolloids, including Acacia, beta-cyclodextrin, gelatin, alginates, pectin, HPMC, and Carbopol, among others.

• Agents that increase buoyancy, such as polypropylene foam powder and ethyl cellulose[48].

Advantages

- High solubility
- First-pass biotransformation that is improved
- Targeted therapy for local conditions in the upper GIT; sustained medication delivery/reduced dosage frequency.
- Lessening of the body's counter-activity.
- More time spent than necessary for effective focus
- Minimized negative intestinal activity.
- Drug delivery at a specified site[49].

Disadvantages

- For medications with gastrointestinal tract solubility or stability issues, floating devices are not practical.
- These systems need a lot of fluid in the stomach to float and function well while delivering drugs.
- Some medications contained in the floating systems induce irritation to the gastric mucosa these drugs are only desirable candidates; they significantly absorb throughout the gastrointestinal tract and undergo significant first pass metabolism[50].

Applications of Floating Drug Delivery Systems

1. Enhanced bioavailability
2. Enhanced first-pass biotransformation
3. Sustained drug delivery/reduced frequency of dosing
4. Targeted therapy for local ailments in the upper GIT
5. Improved receptor activation selectivity
6. Reduced counter-activity of the body
7. Extended time over critical (effective) concentration
8. Minimized adverse activity at the colon
9. Site specific drug delivery[51].

Approaches to Design Floating Dosage Forms

To increase the stomach retention of dose forms, a number of strategies have been investigated, including floating, swelling, sedimentation, and adhesion [52, 53]. (Figure 3)

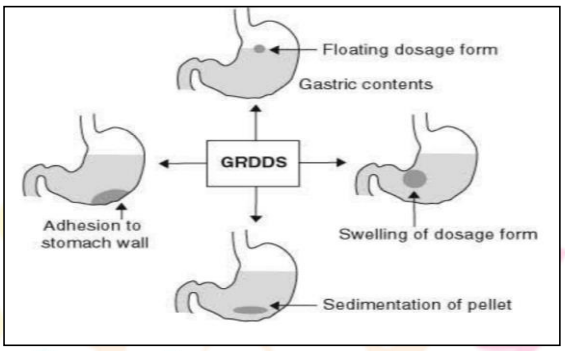

Figure No 5: Different approaches of gastric retention

FLOATING AGENCIES

- Cyclodextrin, sodium alginate, CPC934P, HPMC, MetoloseS.M.100, PVP, HPMC K15, HPMC K4, Acrylic polymer, and Carbopol are examples of hydrochlorides.
- Inert fatty substances, such as long-chain fatty alcohols, beeswax, and fatty acids
- Effervescent substances include di-sodium glycine carbonate (Di-SGC), citric acid, tartaric acid, and sodium bicarbonate.
- Accelerators of the release rate (5%–60%), like lactose and mannitol.
- Release rate retardants (5%–60%), such as magnesium stearate, talc, and dicalcium phosphate
- Agents that increase buoyancy (up to 80%), such as ethyl cellulose[54].

Formulation Methods

- Direct compression technique
- Melt granulation technique
- Melt solidification technique
- Spray drying technique
- Wet granulation technique[55].

Amount of gas forming agent

Although a faster and higher CO2 generation was anticipated, increasing the amount of the gas producing agent (NaHCO3) from 20% to 80% (w/w) did not significantly impact the time to float. However, as the ratio of the gas producing agent to HPMC grew, the drug release increased as well. The HPMC seems to be crucial in delaying medication release. The simpler and quicker water penetration through the tablets led to the increased medication release from the floating tablets coated with higher amounts of gas producing agent and lower amounts of HPMC. In response to a higher gas pressure and concomitant faster drug release, a faster and higher CO2 generation brought on by an increase in effervescent level induced a higher swelling of polymeric membrane. Additionally, their greater porosity or volume inside the polymeric membrane is likely to account for the faster drug release from the floating tablets with higher amounts of gas producing agent. When compared to the lesser porosity produced by the tablets with a low amount of a gas producing agent, this may make it easier for the liquid to dissolve the medication[56,57].

Drug excipient compatibility study

Fourier transform infrared spectroscopy (FTIR)

Instrument was used to determine whether a medicine and its excipients were compatible by examining their interactions. Blends of the drug and excipients' FTIR spectra were compared to the FTIR spectrum of the drug in its simplest form[58].

PRE-COMPRESSION PARAMETER

Angle of repose

A The funnel method was used to calculate the powder blend's angle of repose. The funnel's height was adjusted such that the tip of the funnel barely touched the top of the powder mixture. In order to create a cone with its apex touching the tip of the funnel, the powder mixture was allowed to freely flow through the funnel and to the surface. Angle of repose was measured for the powder cone's diameter, and using the following equation, angle of repose was determined[59]. $\tan \theta = h/r$

Where, $\theta = \tan^{-1}(h/r)$

h = height of pile

r = radius of the base of pile

Bulk density

By pouring a mass of powder into a graduated measuring cylinder and recording the bulk volume, the bulk density was ascertained. The procedure was carried out three times, and the bulk volume was used to determine the mean of the numbers displayed as final volume. The following formula was used to determine the powder's bulk density [60].

$$\text{Bulk density} - \frac{\text{Weight of the powder}}{\text{Bulk volume of powder}}$$

Tapped density

By pouring a mass of powder into a graduated measuring cylinder and recording the bulk volume, the bulk density was ascertained. The procedure was carried out three times, and the bulk volume was used to determine the mean of the numbers displayed as final volume. The following formula was used to determine the powder's bulk density [61].

$$\text{Tapped density-} \frac{\text{Bulk density}}{\text{Taped density}} \times 100$$

Carr's index

Equation was used to get the granules' compressibility index using the Carr compressibility index[62].

$$\text{Carr s Index} - \frac{\text{tapped density} - \text{Bulk density}}{\text{Tapped Density}} \times 100$$

Hausner's ratio

Hausner's ratio is an index of ease with which powder flows, it is related to inter particulate friction, which could be used to predict powder flow properties. It is calculated by following formula[63].

$$\text{Hausner's ratio-} \frac{\text{Tapped density}}{\text{Bulk density}}$$

POST- COMPRESSION PARAMETERS

Thickness

Using vernier callipers, the tablets' thickness was measured. Average results were computed using five tablets. Hardness A tablet's hardness reveals its capacity to tolerate managing mechanical shocks. Using a Pfizer hardness tester, the tablets' hardness was evaluated. The unit of measurement is kg/cm2. Three tablets were chosen at random, and their hardness was measured[64].

Weight variation

To study weight variation twenty tablets of the formulation were weighed using an electronic balance and the test was performed according to the official method. Twenty tablets were selected randomly from each batch and weighed individually to check for weight variation. Percent weight variation was calculated by using the following equation[65].

$$\% \text{ Weight Variation} = \frac{\text{Average Weight} - \text{Individual Weight}}{\text{Average Weight}} \times 100$$

Friability Test

Testing for friability is done to see how well tablets hold up during travel and during packing. Using a revolving drum with a baffle, this entails dropping a sample of tablets repeatedly over a predetermined period of time. For broken tablets and the proportion of tablet mass lost through chipping, the outcome is examined. It's stated as a percentage (%) [66].

$$\%\text{Friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

Friability of tablets less than 1% are considered acceptable.

Differential Scanning Calorimetry (DSC)

Differential Scanning Calorimetry (DSC) experiments were carried out to find out the presence of any interaction among drug and the excipients. Pure drug, 1:1 ratio of drug and polymer, and optimised formulation were subjected to the analysis. About 5-15 mg of sample to be analysed was taken in the pierced DSC aluminium pan and scanned in the temperature range of 50-300 °C. The heating rate was 10°C/min.; nitrogen served as purged gas and the system was cooled down by liquid nitrogen[67].

Drug Content

Determination For drug content determination, 10 randomly selected tablets from each batch were powdered in a mortar. After accurately weighing 10 mg equivalent of the drug from the powdered formulation, this was dissolved in methanol in 100 mL vol. flask and then diluted with 0.1 N HCL to the desired concentration, which was determined by UV-Visible spectrometry. The absorbance of the pure drug neratinib was measured using a UV-Vis spectrophotometer. The absorption maxima of pure drug were found to specify nm[68,69].

Swelling index

The swelling ability of the tablet was determined in 900 ml of acidic medium (0.1 N HCL) at room temperature weighed tablet was immersed in the medium and it was removed periodically from from the medium. after draining the free water, the tablet was measured for weight gain. Swelling Index was expressed by the following equation[70].

$$\text{Swelling index} = \frac{\text{weight of swollen tablet} - \text{Initial weight of tablet}}{\text{Initial weight of the tablet}} \times 100$$

***In-vitro* buoyancy study**

The in vitro buoyancy was determined by as per the reported method. The tablets were placed in a 100ml beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time (FLT). And total duration of time for the dosage form to remain buoyant is called total floating time[71,72].

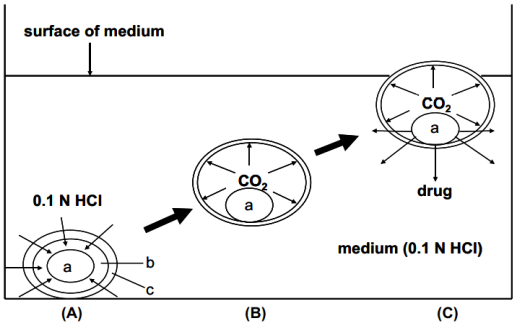

Figure No 6: (A) permeation of medium; (B) gas (CO2) formation and floating; (C) drug release.

Preparation of the standard curve

100 mg of drug was dissolved in small amount of 0.1 N HCL and make the volume up to 100mL with 0.1N HCL, from this primary stock (mg/mL), 10 ml solution was transferred to another volumetric flask made up to 100 mL with phosphate buffer 0.1N HCL. From this secondary stock 0.1, 0.2, 0.4, 0.6, 0.8, 1.0,1.2 mL was taken separately and made up to 10 mL with phosphate buffer 0.1N HCL, to produce 1, 2, 4, 6, 8, 10. µg/mL respectively. The absorbance was measured at specific nm using a UV spectrophotometer[73,74].

In- vitro drug release studies

Drug release studies of the prepared floating tablets were carried out in USP dissolution apparatus II at 37°C±0.5°C, and paddle rotation was 50 rpm. Tablets were placed in 900 mL of 0.1 N HCl solution (pH 1.2), and as, dissolution of 60 mg in 900 mL at 37°C is considered under sink conditions. Suitable sample volumes were withdrawn from the dissolution vessels by with filters at 10,20,30,40,50, and 24 hours. Withdrawn volumes were replaced with fresh medium, and drug content was determined by UV spectroscopy at specific, and the cumulative drug release percentage was calculated[75,76].

STABILITY STUDY

Stability studies adhere to WHO and Harmonisation standards. The stability study is carried out to examine the formulation's physical and chemical integrity[77]. A stability study was conducted on the chosen batch. The release characteristics of the tablets were significantly impacted by environmental factors. The promising formulation was subjected to short-term stability experiments by keeping the tablets in Ziplock bags at 30 to 40 °C and 75% RH for four weeks. The pills were tested for in vitro dissolving profile after a month. Since dissolution study is the evaluating parameter, dissolution profile of the batch under stability study was taken on day 0, i.e., before the start of the study, and then, again it is taken at the end of the study, i.e., after 30 days[78].

Table No: Examples of the marketed products [79,80].

Brand name	Dosage Form	Drug (dose)	Company, country
Madpar	Floating, CR capsule	Levodopa Beserazide	Roche Products, USA
Valrelease	Floting capsule	Diazepam	Hoffmann-laRoche USA
Liquid Gaviscon	Effervescent floting liquid alginate preparation	AI hydroxide Mg carbonate	GlaxoSmithKline, India
Topalkan	Floting liquid alginate preparation	AI-Mg antacid	Piarre Fabre Drug, France
Almagate Flot coat	Floting dosage form	AI-Mg antacid	
Conviron	Colloidal gel forming floating dosage form	Ferrous sulphate	Ranbaxy, India

Cifran OD	Gas-generating floating form	Ciprofloxacin	Ranbaxy
Cytotac	Bilayer floating capsule	Misoprostol	Pharmacia, USA
Glumetza	Layered floating matrix	Metformin	Depomed
ProQuin XR	Layered floating matrix	Ciprofloxacin	Depomed

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REFERENCES

1. Kulkarni, A. and Deb, S., 2019. Dysmenorrhoea. *Obstetrics, Gynaecology & Reproductive Medicine*, *29*(10), pp.286-291.
2. Giudice, L.C., Evers, J.L. and Healy, D.L. eds., 2012. *Endometriosis: Science and Practice*. John Wiley & Sons.
3. Management of dysmenorrhoea Neil Johnson, a University of Auckland, *Department of Obstetrics & Gynaecology, National Women's Health* at Auckland Hospital, Auckland, New Zealand b Fertility Plus, Greenlane Clinical Center, Auckland, New Zealand c Auckland Gynaecology Group, Parnell, Auckland, New Zealand Received 28 June 2005; accepted 13 September 2005. 3.
4. Pakpour, A.H., Kazemi, F., Alimoradi, Z. and Griffiths, M.D., 2020. Depression, anxiety, stress, and dysmenorrhea: a protocol for a systematic review. *Systematic Reviews*, *9*(1), pp.1-6.
5. Thakur, P. and Pathania, A.R., 2021. Relief of dysmenorrhea–A review of different types of pharmacological and non-pharmacological treatments. *Materials Today: Proceedings*. Relief
6. Friederich, M.A., 2017. Dysmenorrhea. In *Lifting the Curse of Menstruation* (pp. 91-106). Routledge.
7. Saltveit, T., 1985. Piroxicam in primary dysmenorrhea. *Acta Obstetricia et Gynecologica Scandinavica*, *64*(8), pp.635-637.
8. Wijma, K., Wijma, B. and Cullhed, S., 1989. Learning-Theoretical Aspects of Primary Dysmenorrhea. *Cognitive Behaviour Therapy*, *18*(3-4), pp.129-136.
9. Dawood, M.Y., 1981. Dysmenorrhoea and prostaglandins: pharmacological and therapeutic considerations. *Drugs*, *22*(1), pp.42-56.
10. Carroquino-Garcia, P., Jiménez-Rejano, J.J., Medrano-Sanchez, E., De La Casa-Almeida, M., Diaz-Mohedo, E. and Suarez-Serrano, C., 2019. Therapeutic exercise in the treatment of primary dysmenorrhea: a systematic review and meta-analysis. *Physical therapy*, *99*(10), pp.1371-1380.
11. Lumsden, M.A., Kelly, R.W. and Baird, D.T., 1983. Primary dysmenorrhoea: the importance of both prostaglandins E2 and F2α. *BJOG: An International Journal of Obstetrics & Gynaecology*, *90*(12), pp.1135-1140.
12. Andersch, B. and Milsom, I., 1982. An epidemiologic study of young women with dysmenorrhea. *American journal of obstetrics and gynecology*, *144*(6), pp.655-660.
13. Bajalan, Z., Moafi, F., MoradiBaglooei, M. and Alimoradi, Z., 2019. Mental health and primary dysmenorrhea: a systematic review. *Journal of Psychosomatic Obstetrics & Gynecology*, *40*(3), pp.185-194.
14. Iacovides, S., Avidon, I. and Baker, F.C., 2015. What we know about primary dysmenorrhea today: a critical review. *Human Reproduction Update*, *21*(6), pp.762-778.
15. Kamuttachat, P. and Thiantongin, P., 2022. Classification of Dysmenorrhea among Students at Ubon Ratchathani Rajabhat University, Thailand According to the Màhaachortàrat Tropical *Journal of Natural Product Research (TJNPR)*, *6*(6), pp.900-905.
16. Bergsjø, P., Jenssen, H. and Vellar, O.D., 1975. Dysmenorrhea in industrial workers. *Acta Obstetricia et Gynecologica Scandinavica*, *54*(3), pp.255-259.
17. Bajalan, Z., Moafi, F., MoradiBaglooei, M. and Alimoradi, Z., 2018. Psychological well-being and first dysmenorrhea: a scientific overview. *J Psychosom Obstet Gynaecol*, pp.1-10.
18. Sadeghi, N., Paknezhad, F., Rashidi Nooshabadi, M., Kavianpour, M., Jafari Rad, S. and Khadem Haghighian, H., 2018. Vitamin E and fish oil, separately or in combination, on treatment of primary dysmenorrhea: a double-blind, randomized clinical trial. *Gynecological Endocrinology*, *34*(9), pp.804-808.

19. Lundstrom, V. and Geijerstam, G. (1983) Treatment of primary Dysmenorrhea Acta *Obstertricia et Gynaecological Scandinavica*,62(113)83-85
20. Ferries-Rowe, E., Corey, E. and Archer, J.S., 2020. Primary dysmenorrhea: diagnosis and therapy. *Obstetrics & Gynecology*, *136*(5), pp.1047-1058.
21. Harel, Z., 2012. Dysmenorrhea in adolescents and young adults: an update on pharmacological treatments and management strategies. *Expert opinion on Pharmacotherapy*, *13*(15), pp.2157-2170.
22. Ryan, S.A., 2017. The treatment of dysmenorrhea. *Pediatric Clinics*, *64*(2), pp.331-342.
23. Woosley, J.A. and Lichstein, K.L., 2014. Dysmenorrhea, the menstrual cycle, and sleep. *Behavioral Medicine*, *40*(1), pp.14-21.
24. Davis, A.R. and Westhoff, C.L., 2001. Primary dysmenorrhea in adolescent girls and treatment with oral contraceptives. *Journal of Pediatric and Adolescent Gynecology*, *14*(1), pp.3-8.
25. Gagnon, M.M. and Elgendy, R., 2020. Comorbid pain experiences in young women with dysmenorrhea. *Women & Health*, *60*(8), pp.946-957.
26. Smith, R.P. and Kaunitz, A.M., 2017. Patient education: Painful menstrual periods (dysmenorrhea) (Beyond the Basics). *Obstetrics, Gynecology and Women's Health. Topic*, *2174*.
27. Wildemeersch, D., Schacht, E. and Wildemeersch, P., 2001. Treatment of primary and secondary dysmenorrhea with a novel'frameless' intrauterine levonorgestrel-releasing drug delivery system: a pilot study. *The European Journal of Contraception & Reproductive Health Care*, *6*(4), pp.192-198.
28. Chueh, H.R., Zia, H. and Rhodes, C.T., 1995. Optimization of sotalol floating and bioadhesive extended-release tablet formulations. *Drug development and industrial pharmacy*, *21*(15), pp.1725-1747.
29. Chidurala, M. and Reddy, R., 2021. Design and Characterization of Combinational Domperidone-Famotidine Floating Drug Delivery System-*In vitro* and In vivo studies. *Ars Pharmaceutica (Internet)*, *62*(2), pp.144-162.
30. Hwang SJ, Park H, Park K. Gastric retentive drug-delivery systems. Crit Rev Their Drug Carrier Syst. 1998;15(3):243–284.
31. Wildemeersch, D. and Schacht, E., 2000. Contraception with a novel 'frameless' intrauterine levonorgestrel-releasing drug delivery system: a pilot study. *The European Journal of Contraception & Reproductive Health Care*, *5*(4), pp.234-240.
32. Lopes, C.M., Bettencourt, C., Rossi, A., Buttini, F. and Barata, P., 2016. Overview of gastroretentive drug delivery systems for improving drug bioavailability. *International journal of pharmaceutics*, *510*(1), pp.144-158.
33. Lodh, H., Sheeba, F.R., Chourasia, P.K., Pardhe, H.A. and Pallavi, N., 2020. Floating drug delivery system: A brief review. *Asian Journal of Pharmacy and Technology*, *10*(4), pp.255-264
34. Bardonnet, P.L., Faivre, V., Pugh, W.J., Piffaretti, J.C. and Falson, F., 2006. Gastroretentive dosage forms: Overview and special case of Helicobacter pylori. *Journal of controlled release*, *111*(1-2), pp.1-18.
35. Murphy, C.S., Pillay, V., Choonara, Y.E. and du Toit, L.C., 2009. Gastroretentive drug delivery systems: current developments in novel system design and evaluation. *Current Drug Delivery*, *6*(5), pp.451-460.
36. Rubinstein, A. and Friend, D.R., 1994. Specific delivery to the gastrointestinal tract. *Polymeric Site-Specific Pharmacotherapy*, *Wiley*, *Chichester*, pp.282-283.
37. Liu, Q., 2010. *Development of a Novel Gastro-Retentive Delivery System Using Alfuzosin HCl as a model drug* (Doctoral dissertation, Temple University. Libraries).
38. Baumgartner, S., Kristl, J., Vrecer, F., Vodopivec, P. and Zorko, B., 2000. Optimisation of floating matrix tablets and evaluation of their gastric residence time. *International Journal of Pharmaceutics*, *195*(1-2), pp.125-135.
39. Singh, B.N. and Kim, K.H., 2000. Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. *Journal of Controlled Release*, *63*(3), pp.235-259.
40. Nayak, A.K., Malakar, J. and Sen, K.K., 2010. Gastroretentive drug delivery technologies: Current approaches and future potential. *Journal of Pharmaceutical Education and Research*, *1*(2), p.1.
41. Sharma, N., Agarwal, D., Gupta, M. K. and Khinchi, M., 2011. A comprehensive review on floating drug delivery system. *International Journal of Research in Pharmaceutical and Biomedical Sciences*, *2*(2), pp.428-441.
42. Bhosale, A.R., Shinde, J.V. and Chavan, R.S., 2020. A Comprehensive Review on Floating Drug Delivery System (FDDS). *Journal of Drug Delivery and Therapeutics*, *10*(6), pp.174-182.
43. Dubey, J. and Verma, N., 2013. Floating drug delivery system: A review. *International Journal of Pharmaceutical Sciences and Research*, *4*(8), p.2893.
44. Patil, P., Baviskar, P. and Saudagar, R.B., 2019. Floating drug delivery system: A comprehensive review. *Journal of Drug Delivery and Therapeutics*, *9*(3-s), pp.839-846.

45. Kotreka, U. and Adeyeye, M.C., 2011. Gastroretentive floating drug-delivery systems: a critical review. *Critical Reviews in Therapeutic Drug Carrier Systems*, *28*(1).
46. Murphy, C.S., Pillay, V., Choonara, Y.E. and du Toit, L.C., 2009. Gastroretentive drug delivery systems: current developments in novel system design and evaluation. *Current Drug Delivery*, *6*(5), pp.451-460.
47. Mayavanshi, A.V. and Gajjar, S.S., 2008. Floating drug delivery systems to increase gastric retention of drugs: A Review. *Research Journal of Pharmacy and Technology*, *1*(4), pp.345-348.
48. Murphy, C.S., Pillay, V., Choonara, Y.E. and du Toit, L.C., 2009. Gastroretentive drug delivery systems: current developments in novel system design and evaluation. *Current drug delivery*, *6*(5), pp.451-460.
49. Streubel, A., Siepmann, J. and Bodmeier, R., 2003. Floating matrix tablets based on low density foam powder: effects of formulation and processing parameters on drug release. *European journal of pharmaceutical sciences*, *18*(1), pp.37-45.
50. Gopalakrishnan, S. and Chenthilnathan, A., 2011. Floating drug delivery systems: A Review. *Journal of Pharmaceutical Science and Technology*, *3*(2), pp.548-554.
51. Tabassum, N., Naqash, A. and Masoodi, M.H., 2011. Floating Drug Delivery System: A Novel Acceptable Approach. *Journal of Pharmacy Research*, *4*(12), pp.4524-4527.
52. Chandel, A., Chauhan, K., Parashar, B., Kumar, H. and Arora, S., 2012. Floating drug delivery systems: A better approach. *International Current Pharmaceutical Journal*, *1*(5), pp.119-127.
53. Arora, S., Ali, J., Ahuja, A., Khar, R.K. and Baboota, S., 2005. Floating drug delivery systems: a review. *Aaps PharmSciTech*, *6*(3), pp. E372-E390.
54. Vijayakumar, A.J.A.Y., Senthilnathan, B. and Ravichandiran, V., 2012. A review article on different types of floating drug delivery systems. *International Journal of Pharmacy and Pharmaceutical Sciences*, *4*(1), pp.45-50.
55. Sungthongjeen, S., Sriamornsak, P. and Puttipipatkhachorn, S., 2008. Design and evaluation of floating multi-layer coated tablets based on gas formation. *European Journal of Pharmaceutics and Biopharmaceutics*, *69*(1), pp.255-263.
56. Choi, B.Y., Park, H.J., Hwang, S.J. and Park, J.B., 2002. Preparation of alginate beads for floating drug delivery system: effects of CO2 gas-forming agents. *International Journal of Pharmaceutics*, *239*(1-2), pp.81-91.
57. Kumar, R., Patil, M.B., Patil, S.R. and Paschapur, M.S., 2009. Formulation and evaluation of effervescent floating tablet of famotidine. *Int J Pharm Tech Res*, *1*(3), pp.754-763.
58. Raza, A., Shen, N., Li, J., Chen, Y. and Wang, J.Y., 2019. Formulation of zein based compression coated floating tablets for enhanced gastric retention and tunable drug release. *European Journal of Pharmaceutical Sciences*, *132*, pp.163-173.
59. Adibkia, K., Hamedeyazdan, S. and Javadzadeh, Y., 2011. Drug release kinetics and physicochemical characteristics of floating drug delivery systems. *Expert Opinion on drug delivery*, *8*(7), pp.891-903.
60. Yadav, P.K. and Chopra, H., 2014. Formulation And Evaluation of Floating Tablet of Metoprolol Succinate with Synthetic Super disintegrant. *International Journal of Pharmaceutical Sciences and Research*, *5*(4), p.1440.
61. Jadi, R.K., Bomma, R. and Sellappan, V., 2016. Development of a new single unit dosage form of propranolol HCl extended-release non-effervescent floating matrix tablets: In vitro and in vivo evaluation. *Journal of Applied Pharmaceutical Science*, *6*(5), pp.112-118.
62. Rahamathulla, M., Hani, U., Alqahtani, A., HV, G., Jafar, M., Osmani, R.A.M., Chidambaram, K., Moin, A. and Shankar, S.J., 2021. 23 Factorial design and optimization of effervescent floating matrix tablet of neratinib. *Journal of Pharmaceutical Innovation*, pp.1-12.
63. Baumgartner, S., Kristl, J., Vrečer, F., Vodopivec, P. and Zorko, B., 2000. Optimisation of floating matrix tablets and evaluation of their gastric residence time. *International journal of pharmaceutics*, *195*(1-2), pp.125-135.
64. Hossain, M.S., Bhuiyan, M.M.K., Banik, S., Hasan, M.A. And Reza, M.S., 2016. Formulation Design and In Vitro Evaluation of Carbamazepine Gastroretentive Floating Drug Delivery System for Oral Application. *Marmara Pharmaceutical Journal*, *21*(1), pp.59-66.
65. Swain, R.P. and Pendela, S., 2016. Formulation and evaluation of gastro-bilayer floating tablets of simvastatin as immediate release layer and atenolol as sustained release layer. *Indian Journal of pharmaceutical sciences*, *78*(4), pp.458-468.
66. Srividya, A.R., Vishnuvarthan, V.J., Murugappan, M. and Dahake, P.G., *International Journal for Pharmaceutical Research Scholars* (IJPRS).
67. Taha, N., Jamil, T. and Akram, M.A., 2019. Formulation, evaluation and in vitro characterization of gastroretentive floating tablet of diclofenac sodium. *Pak. J. Pharm. Sci*, *32*(6), pp.2573-2578.

68. Rahim, S.A., Carter, P.A. and Elkordy, A.A., 2015. Design and evaluation of effervescent floating tablets based on hydroxyethyl cellulose and sodium alginate using pentoxifylline as a model drug. *Drug design, development and therapy*, *9*, p.1843.
69. Meka, V.S., Dharmanlingam, S.R. and Kolapalli, V.R.M., 2014. Formulation of gastroretentive floating drug delivery system using hydrophilic polymers and its in vitro characterization. Brazilian Journal of Pharmaceutical Sciences, 50, pp.431-439.
70. Aundhia, C., Shah, N., Patel, S., Sen, A.K. and Patel, P., 2019. Formulation and Evaluation of Floating Tablet of Norfloxacin.
71. Soppimath, K.S., Kulkarni, A.R., Rudzinski, W.E. and Aminabhavi, T.M., 2001. Microspheres as floating drug-delivery systems to increase gastric retention of drugs. *Drug metabolism reviews*, *33*(2), pp.149-160.
72. Pawar, V.K., Kansal, S., Garg, G., Awasthi, R., Singodia, D. and Kulkarni, G.T., 2011. Gastroretentive dosage forms: A review with special emphasis on floating drug delivery systems. *Drug delivery*, *18*(2), pp.97-110.
73. Rapolu, K., Sanka, K., Vemula, P.K., Aatipamula, V., Mohd, A.B. and Diwan, P.V., 2013. Optimization and characterization of gastroretentive floating drug delivery system using Box-Behnken design. *Drug development and industrial pharmacy*, *39*(12), pp.1928-1935.
74. Upadhyay, P., Nayak, K., Patel, K., Patel, J., Shah, S. and Deshpande, J., 2014. Formulation development, optimization, and evaluation of sustained release tablet of valacyclovir hydrochloride by combined approach of floating and swelling for better gastric retention. *Drug delivery and translational research*, *4*(5), pp.452-464.
75. Li, S., Lin, S., Daggy, B.P., Mirchandani, H.L. and Chien, Y.W., 2002. Effect of formulation variables on the floating properties of gastric floating drug delivery system. *Drug development and industrial pharmacy*, *28*(7), pp.783-793.
76. Patel, A., Modasiya, M., Shah, D. and Patel, V., 2009. Development and in vivo floating behavior of verapamil HCl intragastric floating tablets. *Aaps Pharmscitech*, *10*(1), pp.310-315.
77. Padole, N. and Avari, J., 2021. Synthesis of Silver Nanoparticles for Antibacterial Activity against Staphylococcus Aureus and Escherichia Coli. *Asian Journal of Pharmaceutical Research and Development*, *9*(5), pp.67-73.
78. Padole, N., Chandankhede, H., Deshmukh, R., Chatakwar, P., Dandekar, S. and Baheti, J., 2022. A Review: Phytochemical Investigation and Medicinal Applications of Herb's. *Asian Journal of Pharmaceutical Research and Development*, *10*(6), pp.137-145.
79. Padole, N.N., Majgavali, N.V., Meshram, M.A. and Padole, N.N., synthesis and characterization of silver nanoparticles by chemical route for potential applications: a review.
80. Liu, Q., 2010. *Development of a novel gastro-retentive delivery system using alfuzosin HCl as a model drug* (Doctoral dissertation, Temple University. Libraries.