FORMULATION AND IN VITRO EVALUATION OF FLOATING TABLETS OF HYDROXYPROPYL METHYLCELLULOSE AND POLYETHYLENE OXIDE USING PRAZOSIN HYDROCHLORIDE AS A MODEL DRUG

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Abstract

The drug prazosin hydrochloride as an example, the goal of this work was to prepare and perform test invitro floating tablets of polyvinyl pyrrolidone (PVP) and hydroxypropyl methyl cellulose (HPMC). The floating pills were created using the effervescent technique, which employed sodium bicarbonate as a gas generator. The dry granulation process was used to create the tablets. The impact of HPMC's polymer concentrations and viscosity classes on the release profile of the medication was assessed. The effects of stearic acid and sodium bicarbonate on the floating properties and drug release profile were also investigated. According to in vitro dissolving research findings, raising the concentration of HPMC PVP and MCC may make it possible to preserve the pharmacokinetic profile. Combining sodium bicarbonate and stearic acid had no discernible impact on the medication release profile. The formulations with 20 mg of sodium bicarbonate per tablet showed the anticipated buoyancy, with an overall floating time of more than 24 hours, a floating lag time of around two minutes. The current work shows that prolonged-release floating tablets containing prazosin hydrochloride can be made using polymers such as HPMC, PVP, and MCC coupled as a gas-producing agent with sodium bicarbonate.

Keywords: Floating medication, HPMC, CRDDS, FDDS, Mucoadhesive, Prazosin hydrochloride.

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1. Introduction

As a result of its flexibility in constructing dose forms compared to other routes, the most popular and effective method for controlled drug delivery has been oral. The typical imitate-release dose form is less effective at maintaining the right plasma medication concentration. [1] The notion of oral controlled-release medication delivery devices was developed in response to this problem as well as others like recurrent dosage and unexpected absorption. The length of the medication's action should be determined by the design characteristics of the drug molecules, which is a desirable trait of controlled release delivery systems. [2] Matrix, or reservoir, osmotic pressure, ion exchange resins, changed density, etc. are only some of the mechanical features that can be used to develop systems for the delivery of oral controlled-release drugs. [3] This article provides a concise overview of the present oral controlled system as well as different formulation strategies for the system of controlled release.

Dose form for a controlled release medication

CRDDS is a dose form that delivers one or more medications either systemically or locally to a specific target organ for a set amount of time in a programmed pattern. [4] Oral controlled-release pharmaceutical administration methods are receiving increased attention because of the adaptability of dosage form design.The main challenges for oral drug delivery systems include therapeutically-effective drug delivery, modification of GI transit time, and reduction of first-pass elimination. [5] With less frequent dosing and fewer side effects, the controlled-release medication offers better maintenance of the appropriate and effective drug level over a longer period of time.

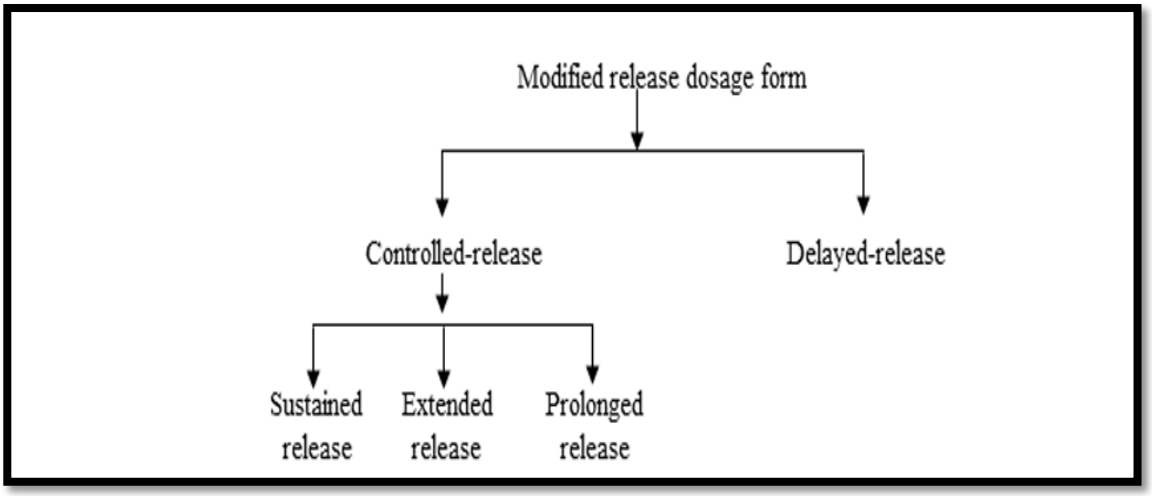


Fig.2 Classification of modified release dosage form

Floating medication transport system

The term "hydrodynamically balanced system" (HBS) is sometimes used to describe drug transport systems that float. The drug is eliminated from the body at a controlled rate while the body is at rest on the stomach contents [6]. The remainder of the drug's system is emptied when it is released into the stomach. As a result, the oscillations in plasma drug concentration are better managed, and GRT is raised. To prevent medications from leaving the stomach too quickly, FDDS uses drug carriers that float in gastric fluid. By extending the release interval, it effectively increases the bioavailability of the medicine. Making the dose form less dense than the stomach liquids allows it to float on them, which is the primary notion of FDDS. FDDS, which are hydrodynamically regulated low-density devices with enough buoyancy to float over and remain buoyant in the stomach's contents, do not significantly slow down the rate of gastric emptying. [7]. The limited

absorption time in the upper gastrointestinal tract presents numerous opportunities for floating drug delivery of medicines with low bioavailability[8,9]. This can be summed up as a sustained drug delivery mechanism because it can linger in the stomach for a very long time.

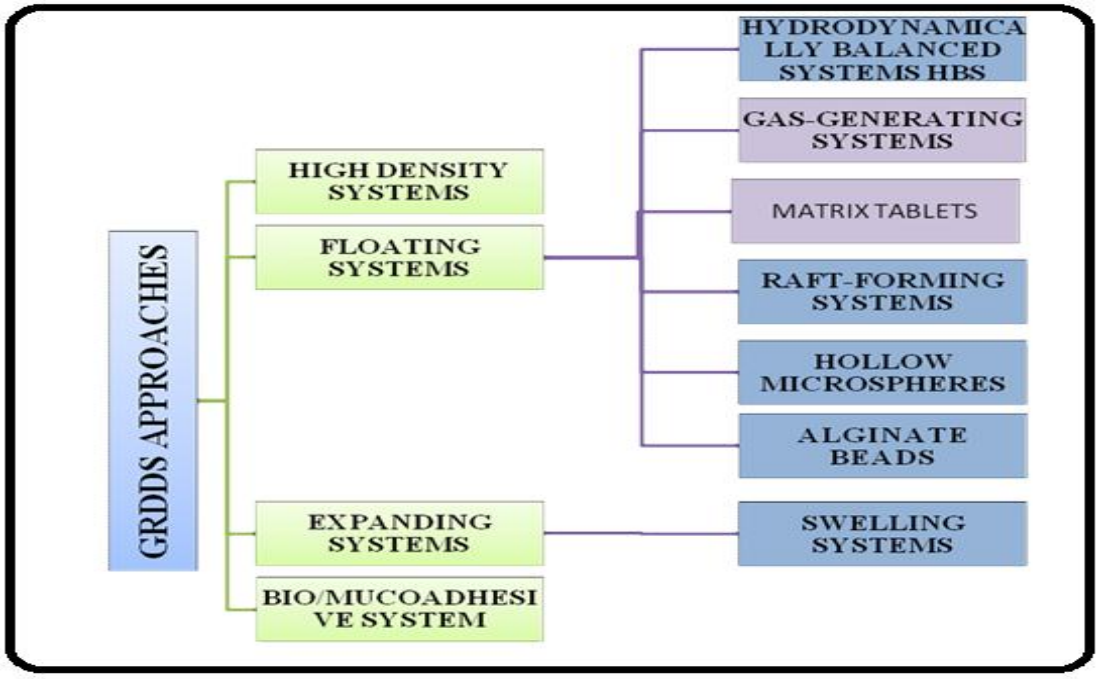


Fig.1 Systemic approaches of various formulation of GRDDS

Mechanism of floating system

There have been several attempts to prolong the holding duration by keeping the dose in the stomach. These initiatives include implementing floating dosage forms., including those that produce gas, swell or expand, are mucoadhesive, high-density, or have changed shapes. They also include the co-administration of medications that delay stomach emptying. [10] The floating dose formulations have been the ones that have been used the most frequently. While floating on the stomach's contents, the medication is gradually and at the desired rate expelled from the body. Once the drug has been discharged, the stomach's remaining digestive system is emptied. [11] GRT is boosted as a result, and the fluctuations in plasma medication concentration are better managed. The dose form's buoyancy on the surface of the meal must be maintained at a minimum level in order to properly apply the buoyancy retention principle (F). The floating force kinetics have been quantified in the literature using a special instrument for estimating the resulting weight. [12] The device constantly gauges the F-equivalent force necessary to maintain the submerged object's position (over time). When F is in the positive range, the object floats more easily.In order to prevent the detrimental consequences of unanticipated oscillations in intragastric buoyancy capacity, In terms of the stability and duration of the floating forces generated, this gadget aids in improving the FDDS.

F = F buoyancy - F gravity = (Df - Ds) gv

Where, F= total vertical force Df = fluid density Ds = object density
v = volume and g = acceleration due to gravity.

Designing Floating Medication Delivery Systems: Approaches [13,14]

I. The amount of time it takes for the tablet to surface on the dissolution liquid is known as the floating lag time and can be expressed in seconds or minutes.

II. For this calculation, we used USP II devices (paddles) to stir a sample of simulated gastric juice (pH 1.2 without pepsin) at 50 or 100 rpm, at a temperature of 37.2^{0}C. Drug dissolution and retention in suspension in vitro. Regular sampling ensues, after which the samples' drug content is examined.

III. Change in dosage form in the GIT is tested by X-ray or gamma-scintigraphic imaging for in-vivo gastro-retention assessment. The pills are also examined for hardness, weight fluctuation, etc.

2. Material and Methods

Prazosin Hydrochloride is a drug indicated or used to treat hypertension and lower blood pressure It is a floating tablet form of a selective alpha-adrenergic receptor blocking medication and counteracts nor-epinephrine outflow and reduces post-synaptic adrenergic responses. [15] Aside from enlarged prostates and PTSD-related nightmares, it is also used for these conditions. It was first authorised by the FDA in 1988 and sold by Pfizer. Prazosin was first used in 1974 after being patented in 1965. It was accessible as a generic drug. It is a derivative of quinazoline. Its chemical formula is $C_{19}H_{21}N_5O_4$.HCl, Prazosin may be used either on its own or in conjunction with other drugs. [16]

Tablet preparation method [17]

1. method of direct compression [18]

All the components were combined in a pestle motor using the direct compression method (in decreasing order of the quantity utilised). This mixture was then triturated and put through sieve number 10. The powder was crushed directly to create tablets after passing through a sieve.

2. Wet granulation method [19,20]

In the wet granulation process, each component was combined in a pestle and mortar in decreasing order of the amount utilised. Granules were then made using a 10% w/v solution of PVP in ethyl alcohol. Granules were retained at filter number 16 after passing through sieve number 12. Granules were then heated for three hours at 70°C in a hot air oven to begin the sublimation process. The process began with the creation of porous granules, which were then mixed with 1% magnesium stearate before being compacted into tablets.

Table no.1 -Preparation of placebo with different concentration of excipients.

S.No	Ingredients	F1	F2	F3	F4	F5
01	HPMC	50	75	100	-	-
02	Carbopol	50	25	25	100	125
03	MCC	50	75	85	100	50
04	Sodium bicarbonate	60	50	20	60	60
05	PVP	10	10	10	10	15
06	Citric acid	20	10	05	20	40
07	Magnesium stearate	10	05	05	10	10

*All the tablet are prepared by direct compression method

Table no 2. creation of a medication formulation that is optimum

S.No.	Ingredient	F1	F2	F3
1	HPMC	50	75	100
2	Carbopol	50	25	25
3	MCC	50	75	85
4	$NaHCO_3$	60	50	20
5	PVP	10	10	10
6	Citric Acid	20	10	05

7	Magnesium stearate	10	05	05

Analysis of floating tablet of prazosin hydrochloride

(I) Physical Appearance

Prazosin hydrochloride is a White or tan with a yellow cast in appearance.

(II) Melting Point

Melting point equipment is used to determine the melting point of prazosin hydrochloride. The apparatus's sealed capillary is filled with prazosin hydrochloride. The sample will then be heated as the temperature rises, and the sample will be monitored to determine when the solid will become liquid. The temperature range begins at the first temperature of the phase shift and concludes at the last temperature of the phase shift, as determined by visual examination.

Melting Point: 258-264^{0}C (with decomposition)

(III) Studies on solubility

Solubility is the ability of two or more compounds to interact in a way that results in a stable molecular dispersion. Prazosin Hydrochloride's solubility in various solvents has already been investigated. At room temperature, a specific amount of the medication (10 mg) was dissolved in 10 ml of each of the studied solvents and solely visually inspected. Drugs are 0.5 mg/ml water-soluble and just slightly soluble in isotonic saline.

(IV) Preparation of dilutions

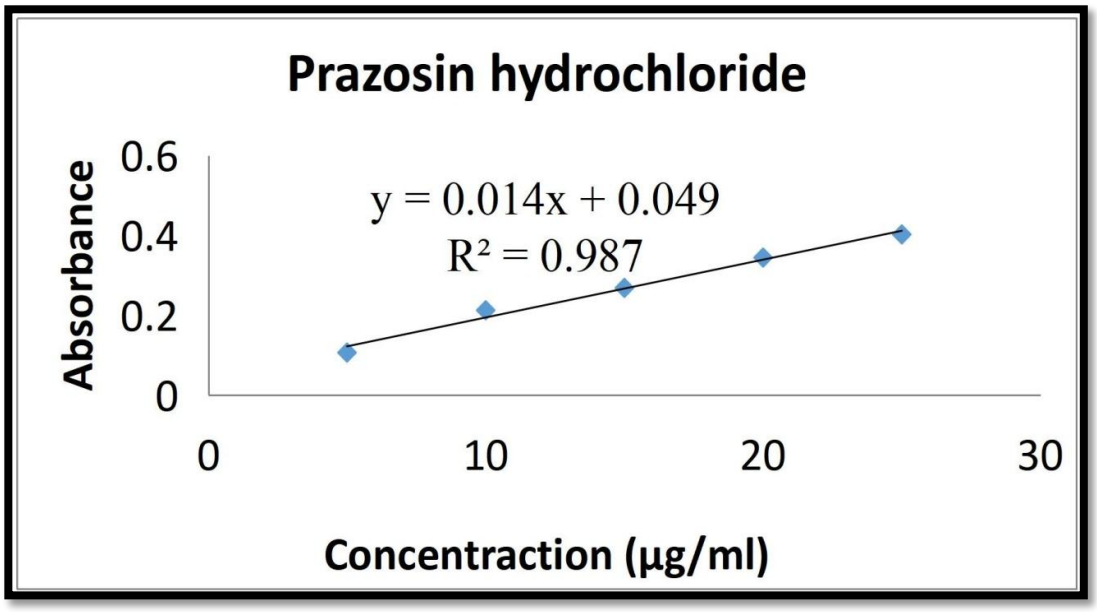
Concentrated solutions 5, 10, 15, 20, 25 µg/ml were prepared by further diluting the stock solution by same medium (0.1N HCl). Absorbance is recorded by using a UV spectrophotometer at 246nm. The amount of drug released was determined from the equation

Y =0.014x+0.049, where Y stands for absorbance.

Table 3- Absorbance curve of Prazosin Hydrochloride 0.1 N HCL at246nm.

S.No.	Dilution(µg/ml)	UV absorbance
01	5µg/ml	0.106
02	10 µg/ml	0.212
03	15 µg/ml	0.268
04	20 µg/ml	0.346
05	25 µg/ml	0.402

Fig.2 Graph of calibrationcurveofprazosinhydrochloride Floating tablet



Equation of line Y = 0.014x +0.049, and R2 value of 0.987 obtainedbycurve was utilized for evaluating drug release graph.

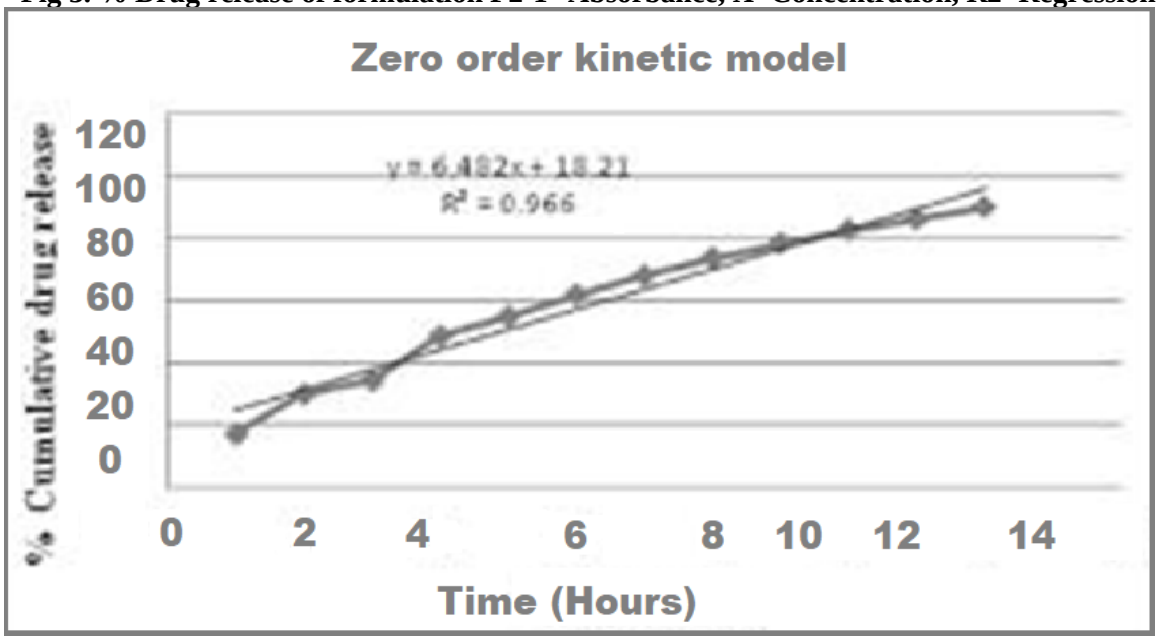
(V) Investigation of drug release in vitro

The best optimized formulation F2 underwent an invitro drug release study. The release was measured with a buffer solution of 0.1N HCl(pH 1.2).

TableNo.4 Percentage of floating drug delivery formulation

S.No.	Time (hrs)	% Drug release
01	1hr	17.08
02	2 hr	28.89
03	3 hr	33.37
04	4 hr	47.62
05	5 hr	55.71
06	6 hr	62.86
07	7 hr	68.78
08	8 hr	72.51
09	9 hr	79.31
10	10 hr	81.62
11	11 hr	87.22
12	12 hr	88.90

Fig 3. % Drug release of formulation F2 Y=Absorbance, X=Concentration, R2=Regression



Evaluation of flow property of Granules
Precompression parameters
Angle of Repose:
It is described as the greatest angle that may be made between the horizontal plane and the surface of the powder pile. The angle of repose is a useful tool for calculating the frictional force in loose powder or grains.

S. No.	Angle of Repose	Type of Flow
01	<20	Excellent

02	20-30	Good
03	30-34	Passable
04	>34	Very poor

Table no 5. Standard values of Angle of Repose to indicate flow property of powder

Table no.6Angle of repose of powder/ granules

F1	F2	F3
34	28	26

Density in bulk form:
It is represented as g/cm^3 and is calculated by dividing the volume of the bulk by the mass of the powder. It is employed to assess the powder's bulkiness. Bulkiness is inversely proportional to bulk density, also known as specific bulk volume.

Table no.7 Bulk density of the powder/ granules

F1	F2	F3
0.40	0.44	0.52

Tapped Density:
A minimum tapped density was calculated by putting a graduated cylinder carrying a specified quantity of powder on mechanical tapping equipment and running it for a predetermined number of taps (100) or until the powder bed volume reached a particular volume. The final tapped volume of powder or granules and the weight of the medicine in the cylinder are used to calculate the tapped density.

Table no.8 Tapped density of powder/ granules

F1	F2	F3
0.65	0.58	0.60

Carr's index (or) % compressibility:
It is sometimes referred to as the compressibility index because it is used to determine the compressibility of a powder. Powder particles that are more compressible have less flowing characteristic. Carr's index is also given as a percentage.

Table no.9Carr's compressibility index and the powder's flow characteristics are related.

S.No.	C. C. I. %	Flow Property
01	5-15	Excellent
02	12-16	Good
03	18-21	Fair to passable
04	23-35	Poor
05	33-38	Very poor
06	>40	Very very poor

3. Result and Discussion

The goal of this work was to develop and assess in vitro floating tablets of polyvinyl

pyrrolidone (PVP) and hydroxypropyl methyl cellulose (HPMC) using prazosin hydrochloride as a model medication. The effervescent method and dry granulation process were used to create the tablets. Investigations were conducted on how sodium bicarbonate and stearic acid affected the drug release profile and floating characteristics. The formulations using 20 mg of sodium bicarbonate per tablet demonstrated the expected buoyancy, with a floating lag time of around 2 minutes and a total floating time of more than 24 hours. CRDDS is a dose form that constantly delivers one or more medications in a predefined sequence to a specific target organ, either systemically or locally.

A floating drug delivery system (FDDS) is a low density, hydrodynamically controlled, buoyant device that can float above the contents of the stomach for a long time without slowing down the rate at which the stomach empties. As a result of the narrow absorption window of the upper gastrointestinal tract, it provides a variety of uses for medications with low bioavailability. To keep the dose form in the stomach, methods for floating drug delivery (FDDS) have been used. These FDDS have a bulk density that is lower than that of gastric fluids and have the ability to float without slowing down the gastric emptying rate. In the literature, a novel device for measuring resultant weight has been presented in order to assess the dynamics of the floating force. The device calculates the force in units of F that is necessary to keep the submerged object submerged over time. One strategy for creating a floating drug delivery system is to use floating lag time, which measures how long it takes for the tablet to appear on the surface of the dissolution media and is measured in seconds or minutes. Prazosin Hydrochloride is a selective alpha-adrenergic receptor blocking drug used to treat hypertension, enlarged prostate, and post-traumatic stress disorder (PTSD) nightmares. It is a quinazoline derivative and its molecular formula is $C_{19}H_{21}N_5O_4$.HCl. Tablet preparation methods include direct compression and wet granulation. USP II devices churning in simulated gastric fluid at 37.2^0C determine in-vitro drug release and floating time. X-ray or gamma- scintigraphic examination is used to assess in-vivo gastro-retention. The wet granulation method involves mixing ingredients together in a pestle motor and preparing granules with 10% w/v solution of PVP in ethyl alcohol. The granules are then placed in a hot air oven for 3 hours at 70 °C for sublimation. Porous granules are then blended with 1% Magnesium stearate and the tablet is compressed andthree precompression properties are Tapped Density, Bulk Density, and Angle of repose.

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