International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 3 May-June 2022, pp: 1379-1392 www.ijprajournal.com ISSN: 2456-4494

Formulation and Evaluation of Floating Tablet of Anti-Hypertensive Drug

Somprabha Madhukar*, Dr.Ritesh Jain, Mrs.Anju Mishra
School of Pharmacy ,Chouksey Engineering College,Bilaspur,C.G

Submitted: 26-05-2022 Revised: 03-06-2022 Accepted: 07-06-2022

ABSTRACT
Objective: This study aims to formulate a floating tablet of amlodipine by direct compression method using different concentrations of the drug.
Methods: in this study, six formulations of amlodipine floating tablets were prepared [mixture of amlodipine, sodium bicarbonate, hydroxypropyl methylcellulose (HPMC) K15M, HPMC K100M, Carbopol 934P, MCC] by direct compression method. The pre-compressed mixtures were then evaluated for various parameters such as angle of repose, bulk density, tapped density, Carr's compressibility index, and Hausner's ratio. After compression, tablets were subjected to several tests like Drug content uniformity (%), Disintegration times (sec), floating behavior of tablets, tablet thickness, hardness test, friability test, weight variation, and in vitro dissolution test. In addition, the optimum formulation was evaluated for differential scanning calorimetry (DSC) tests and particle size and morphology analysis (SEM).
Keywords – Amlopine, HPMC, Differential scanning calorimetry(DSC).

I. INTRODUCTION

Pharmaceutical products for oral delivery are available upon both prescription and over-the-counter (Gupta 2013). The oral route of administration is the most popular and effective for traditional drug delivery. Advantages include convenience, ease of administration, enhanced dosage form design flexibility, ease of production, and low cost. Solutions, suspensions, powders, pills, and capsules are some of the pharmaceutical formulations available. Because the majority of them are solids, they are given in solid dose form. solid dosage forms provide the best protection for medications against temperature, light, oxygen, and stress, during transit(Curry1983).

hypertension has becomea major public health problem around the world.(Oparil, Zaman, and Calhoun 2003). Antihypertensive medicines are a group of compounds that have been developed to prevent, regulate, or treating hypertension. Antihypertensive medication classes are structurally and functionally distinct. The majority of hypertensive people have primary (or essential) hypertension, which implies their blood pressure isn't caused by anything else. Treatment aims to control blood pressure, avoid end-organ damage (cerebrovascular, cardiovascular, and renal), and reduce the chance of early mortality. (Elliott 2012). Calcium channel blockers (CCBs) were first discovered for the therapy of coronary heart disease (CHD) approximately 35 years ago, but their utility in the treatment of hypertension was immediately recognized (HTN). Angina, peripheral vascular disease, and various arrhythmic disorderswere among the first indications, in addition to HTN. (Triggle 2007). Calcium channel blockers, like amlodipine (AD), are a class of medicine. They adhere to targeted receptors slowly and steadily, leading in a toooth initiation of action and 24-hour blood pressure management. The use of these longer-acting calcium channel blockers on a once- daily routine improves patient compliance and reduces side effects. (Palma-Gámiz 1997)and it is well tolerated as monotherapy and in combination with other antihypertensive drugs (Julius 1988). Amlodipine is commonly used in the treatment of heart diseases like angina and hypertension (Anon n.d.).

Floating Drug Delivery System - Drug delivery systems that float or are hydrodynamically balanced have a lower bulk density than gastrointestinal fluids. The tablet remains buoyant for a longer period as a result of this property, allowing its medicine to be released slowly and at the desired rate. Weight measurements and expanding characteristics, on the other hand, are two more important aspects of the tablets' buoyant capacities. Polymers play a vital role in modulating drug release in such systems. An effervescent component is sometimes added when it comes into contact with the acidic stomach secretions, which release CO_2. The released gas becomes imprisoned in the gelled hydrocolloid, which causes the tablet

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 3 May-June 2022, pp: 1379-1392 www.ijprajournal.com ISSN: 2456-4494

to float higher(Singh and Kim 2000). Different hydrophilic and hydrophobic polymers, and also effervescing substances includingsodium bicarbonate and citric acid, were used to make the tablets utilizing the direct compression method(Pare, Yadav, and Patil 2008).

Immediate-release dosage forms - Immediate release dosage forms are conventional-dosage forms that dissolve in the gastrointestinal tract without delaying or extending the drug's dissolution or absorption. Its solubility of immediate medicine release dosage forms is improved as they dissolve quickly after delivery. These dosage forms frequently release (dissolve) the medication in a single action, which means that the drug is released quickly and then travels through the mucosal membrane into the body, reaching the maximal plasma level in a short time.(Hamid and Merchant 2006; Reddy et al. 2011; Sood et al.2012).

DRUG - AMLODIPINE

Amlodipine is a blood pressure medication that also relieves chest pain. It expands blood vessels, which lowers blood pressure. Amlodipine improves blood flow to the heart muscle, which helps to relieve angina pain. To treat hypertension and coronary artery disease, it can be used alone or in combination with other drugs. Amlodipine can be taken by adults and children aged 6 to 17. (Gradman et al.2010).

Chemical structure -

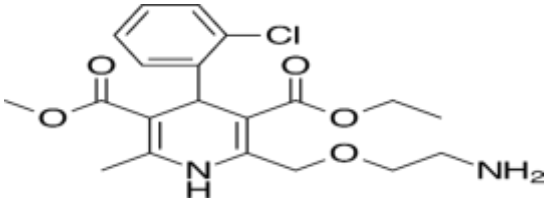


Figure 1: Structure of Amlodipine Besylate

formula: $C_{20}H_{25}ClN_2O_5$

IUPAC name – 3-ethyl 5- methyl 2-[(2-aminoethoxy) methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate

Molecular weight: 408.88 gm/mol **Description:** White powder

Melting point: 195-2040°

Solubility: Slightly soluble in water, freely soluble in methanol, sparingly soluble in ethanol, slightly soluble in 2-propanol.

Therapeutic category: Antianginal, Anti-hypertensive

Half-life: 30 – 35 hours

PH - 1-6 at 370 ^{0}C

pKa - 8.6

Mechanism of action: Amlodipine is a dihydropyridine calcium antagonist that stops calcium ions from passing across the membrane into vascular smooth muscle and cardiac muscle. Extracellular calcium ions must enter cardiac muscle and vascular smooth muscle cells through specific ion channels for them to contract. Within the physiologic pH range, amlodipine is an ionised mionized, and its kinetic interaction with the calcium channel receptor is charactercharacterizedggish rate of association and dissociation with the receptor binding site, resulting in a slow onset of effect. (Anon n.d.; Tripathi 2003).

Pharmacokinetics:

1. **Absorption:**Afteroraladministration of therapeutic doses, amlodipine is well absorbed with peak blood levels between6-
12 hours post-dose. Absolute bioavailability has been estimated to be between 60 and 80%.
2. **Distribution:** In-vitro studies have shown that approximately 97.5% of circulating amlodipine is bound to plasmaproteins.
3. **Metabolism:** Amlodipine is extensively metabolized by the liver to inactive metabolites.
4. **Excretion:** 10% of the parent compound and 60% of metabolites are excreted in the urine.

Indications: Hypertension and prophylaxis of angina.

Dosage and administration:

Adult recommended starting dose - 5 mg once daily with a maximum dose of 10 mg once daily. Small, fragile, or elderly patients or patients with hepatic insufficiency may be started on 2.5 mg once daily. Pediatric starting dose: 2.5 mg to 5 mg once daily. **Side effects**: Most side effects are mild or moderate (Hermida et al. 2008; Vukadinovic et al. 2019) are tiredness, extreme sleepiness, stomach pain, drowsiness,skin rash, swelling of legs or ankles, flushing, headache, peripheral edema, pulmonary oedemafatigue, nausea, dizziness, flushing (hot or warm feeling in your face), arrhythmia (irregular heartbeat), Heart palpitation (very fastheartbeat).

Contraindications- Amlodipine is contraindicated in patients with known hypersensitivity to amlodipine or its dosage form components. Cardiogenic shock, severe aortic stenosis, unstable angina, severe hypotension, heart failure, or hepatic impairment are other contraindications to taking

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 3 May-June 2022, pp: 1379-1392 www.ijprajournal.com ISSN: 2456-4494

amlodipine. The cardiogenic shock causes the heart to stop pumping adequately, which is exacerbated by calcium ions not being allowed to enter cardiac cells. In patients with severe aortic stenosis, amlodipine may cause ventricular collapse and dysfunction. Amlodipine raises cardiac contractility instinctively in unstable angiwhichthat increases myocardial oxygen demand and increases ischemia.(Agarwal, Flatt, and Khouzam 2018). Patients have heart failure may experience pulmonaredemama, shortness of breath, and dyspnoea with amlodipine (De Vries, Van Veldhuisen, and Dunselman 2000).

Toxicity-As a therapeutic option, amlodipine overdose and toxicity can cause serious vasodilation, hypotension, and reflex tachycardia. Prolonged systemic hypotension can lead to shock and even death. Electrocardiographic data, vital signs, renal function, urine output, and electrolytes must all be carefully monitored during such an overdose.(Agarwal et al. 2018; St-Onge et al. 2014).

MATERIAL – Amlodipine, sodium bicarbonate, magnesium stearate, MCC, Carbopol 934P, talc hydroxypropyl methyl cellulose K100M, hydroxypropyl methyl cellulose K15M, citric acid, Aerosil, Poly-vinyl Pyrrolidine K30.

II. IDENTIFICATION OF MATERIALS –

METHODS

Floating tablets containing Amlodipine were prepared by direct compression technique using varying concentrations of different grades of polymers with Sodium bicarbonate and citric acid. All of the components were precisely weighed and sieved using different mesh sizes. Then, except for Magnesium stearate, all other materials were evenly combined in a glass mortar. Magnesium stearate and purified talc (1% w/w) were added after adequate mixing of the medication and other components, and the mixture was stirred for another 2-3 minutes before being crushed using a single punch tablet machine. For all formulations, the tablet weights were keptconstant.

Table no. 1 - COMPOSITION OF ALL THE FORMULATIONS (F1 –F6)

INGREDIENTS	BATCH F1	BATCH F2	BATCH F3	BATCH F4	BATCH F5	BATCH F6
Amlodipine	10	10	10	10	10	10
Aerosil	5	5	5	5	5	5
Talc	5	5	5	5	5	5
Magnesium Stearate	10	10	10	10	10	10
Polyvinyl Pyrrolidine K30	10	10	10	10	10	10
Citric Acid	30	30	30	30	30	30
Sodium Bicarbonate	60	60	60	60	60	60
MCC	50	50	50	70	50	60
Carbopol 934P	70	50	50	50	60	50
HPMC K15M	50	70	50	50	60	60
HPMC K100M	50	50	70	50	50	50
TOTAL WEIGHT	**350**	**350**	**350**	**350**	**350**	**350**

*All the quantities are in mg

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 3 May-June 2022, pp: 1379-1392 www.ijprajournal.com ISSN: 2456-4494

CHARACTERIZATIONOF FLOATING AMLODIPINE TABLETS PREFORMULATION PARAMETERS –The quality of tablets, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all of these can affect the characteristics of blends produced. The various characteristics of blends were tested as per Pharmacopoeia.

1. **Solubility Profile** - Amlodipine solubility profile determination. The selected drug's solubility profile was determined. Wateris slightly soluble, methanol is freely soluble, ethanol is sparingly soluble, and 2-propanol is slightlysoluble.

Table no. 2 - Solubility Profile of Amlodipine

S.n.	Solvent	Solubility
1	Water	Slightly soluble
2	2 propanol	Slightly soluble
3	Methanol	Freely soluble
4	Alcohol	Sparingly soluble

2. **Angle of repose** - The frictional force in a loose powder can be calculated using the angle of repose. The maximum angle that the powder pile's surface can produce with the horizontal line is established. If more powder is added to the pile, it will slide down the sides until the mutual friction between the particles equals the gravitational force, resulting in a surface angle. The fixed funnel approach was used to determine the angle of repose. On a level horizontal surface, a funnel was put above graph paper with its end at a particular height (h). The mixture has been gently poured through the funnel until the conical pile's peak just touches the funnel's tip.The radius (r) of the base of the conical pile was measured. The angle of repose was calculated using the following formula: (Pawar and Dhavale 2014; Sinha, Agrawal, and Kumria2005)

$\tan \theta = h / r$

Tan θ = Angle of repose h = Height of the cone,
r = Radius of the cone base. (Damodharan, Manimaran, and Sravanthi 2010)

Table no. 3 - Angle of Repose values (as per USP)

The angle of Repose (θ)	Nature of Flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

3. **Bulk density (**Pb**)** - Density is defined as weight per unit volume. Bulk density is defined as the mass of the powder divided by the bulk volume and is expressed as gm/cm3. The bulk density of a powder is determined largely by particle size distribution, particle shape, and particle adhesion. Bulk density has a big impact on the size of containers needed for raw material and mix handling, shipping, and storage. It's also crucial in size mixing machines. (Rahim, Carter, and Elkordy 2015). The bulk density was calculated using the formula:

Bulk Density = M / Vo

Where M = weight of a sample Vo = apparent volume ofpowder

4. **Tapped density** - Following the procedure for measuring bulk density, the cylinder containing the sample was tapped witha

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 3 May-June 2022, pp: 1379-1392 www.ijprajournal.com ISSN: 2456-4494

suitable mechanical tapped density tester capable of producing 100 drops per minute, and the procedure was repeated until the difference between successive measurements was less than 2%, and the tapped volume, V, was measured to the nearest graduated unit. Using the formula, the tapped density in grams per L was obtained (Anepu, Duppala, and Sundari2017).

Tap = M / V Where Tap= Tapped Density M = Weight of sample

V= Tapped volume of powder

5. **Measures of powder compressibility** - The Compressibility Index (Carr's Index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. It is a measure of the relative importance of inter-particulate interactions as such. Such interactions are less important in a free-flowing powder, and the bulk and tapped densities will be closer in value. There are usually more interparticle interactions in poorer moving materials, resulting in a larger gap between bulk and tapped densities. The Compressibility Index, which is determined using the methods below, reflects these variations (Damodharan et al.2010)

Carr's Index = [(tap - b) / tap] × 100 Where, b = Bulk Density

Tap = Tapped Density

Table no. 4 - Carr's index value (as per USP)

Carr's index	Properties
5 – 15	Excellent
12 – 16	Good
18 – 21	Fair to Passable
2 – 35	Poor
33 – 38	Very Poor
>40	Very-very poor

6. **Hausner ratio** - Hausner's ratio can be determined as the ratio of tapped density to the bulk density of the powders and as the resulting equation (Jagdale et al. 2009; Shahi et al.2014).

Hausner ratio = tapped density / bulk density

POST-COMPRESSION PARAMETERS

1. **General appearance** - The general appearance of tablets, visual identity, and overall 'elegance' is essential for consumer acceptance, control of lot-to-lot uniformity and general tablet uniformity, and for monitoring the production process. The control of general appearance involves the measurement of attributes such as a tablet's size, shape, color, presence or absence of oodor taste, surface textures, physical flaws, andconsistency.
2. **Size and Shape** - The type of tooling determines the shape and the dimensions of compressed tablets during the compression process. Tablet thickness varies with changes in die fill, particle size distribution, and packing of the powder mix being compressed, as well as tablet weight, at constant compressive pressure, while thickness varies with variation in compressive load at a constant die fill. Only if the tablet granulation or powder mix is suitably uniform in particle size and particle size distribution, if the punch tooling is of consistent length, and if the tablet press is clean and in excellent operating order will tablet thickness be consistent from batch to batch or within abatch.

3. **Tablet thickness** - The thickness of the tablet was set using a Verniercaliper. The average results were determined using twenty floating tablets. When it comes to recreating the look, tablet thickness is important. When it comes to reproducing appearance, tablet thickness is important. The average thickness of the core and coated tablets is determined and the variance is shown (Jagdale et al.2009).
4. **Hardness test** - Hardness of a tablet is defined as the force applied across the diameter of the tablet to break the tablet. The hardness of the tablet determines its resistance to chipping, abrasion, or breaking during storage transformation and handling before use. The hardness of three tablets was measured using a

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 3 May-June 2022, pp: 1379-1392 www.ijprajournal.com ISSN: 2456-4494

Monsanto hardness tester for each formulation, and the average was computed and reported with deviation (Alhamdany and Abbas 2018; Damodharan et al. 2010)

5. **Friability** – It is measured bythe mechanical strength of tablets. Roche friabilator was used gold-palladium by using Sputter Coater, after fixing the sample in individualstabs to determine the friability. Pre-weighed tablets 20 tablets were placed in the friabilator. The tablets were rotated at 25 rpm for 4 minutes (100 rotations). the tablets were then dusted and reweighed. Tablets that lose no more than 1% of their weight are typically deemed to be acceptable. The following equation was used to compute percentage friability. (Cifuentes et al. 2013; El-Bagory et al. 2012; Pawar et al. 2013).

% Friability = $[(W_1-W_2) / W] \times 100$ Where W_1 = Initial weight of four tablets

W_2 = Weight of the four tablets after testing

6. **Weight variation** - To study the weight variation, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. If the weights of not more than 2 of the floating tablets differ from the average weight by more than the percentage indicated in the USP, and no tablet differs in weight by more than double that percentage, the standards are followed.(Ashok and Damodar 2013; Chowdhury 2012).

The percent deviation was calculated using the following formula.

% Deviation = (Individual weight – Average weight / Average weight) ×100

pharmacopeial specifications for tablet weight variation.

7. **Disintegration Time** - The test is carried out on the 3 tablets using the apparatus specified in USP distilled water at 37 ^{0}C ± 2 ^{0}C was used as a disintegration media and the time in second taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured inseconds.
8. **Particle size and Morphology analysis (SEM)** - The particle size of microparticles was determined using the optical microscopy method. Approximately 100 microparticles were counted for particle size using a calibrated optical microscope Surface morphology of the microsphere was determined by Scanning Electron Microscope (SEM). The microparticles were coated uniformly with
9. **Differential scanning calorimetry (DSC)** - The possibility of drug-excipient interaction was further investigated bydifferential scanning calorimetry. DSC curve for each pure powder of amlodipine, hydroxypropyl methylcellulose (HPMC) K15M,K100M, in addition to the physical mixture of the optimum formula of amlodipine in the presence of polymers (Precompression) and compressed tablet (post-compression) analysis, was implemented using DSC instrument. The samples were accurately weighed and heated in a sealed aluminum pan at a rate of 10 °C/min. within a 10 and 250 °C temperature range under a nitrogen flow of 40 ml/min (Pawar and Dhavale2014).

10. **In vitro Buoyancystudies** - These studies can be applicated by taking tablets (n = 3) and place in 1000 ml of 0.01 N HCl in a USP type II dissolution apparatus (37±0.5 °C, 50 rpm). The time desired for tablets to float at the topmost of the medium was considered as floating lag time. The interval of time the tablet continuously kept on the surface was considered the total floating time (Biswas et al. 2002; Sungthongjeen, Sriamornsak, and Puttipipatkhachorn 2011). Formula indicated that floating tablets made with a greater viscosity grade of hydroxypropyl methylcellulose (HPMC) K100M had a longer floating lag time and total floatation duration of more than 24 hours than those made with a lower viscosity grade of hydroxypropyl methylcellulose (HPMC) K100M. It was most likely due to increased polymer entanglement and gel strength, as well as a reduced effective molecular diffusion area inside a high viscosity hydroxypropyl methylcellulose grade compared to a low viscosity grade (HPMC) (Patel, Patel, and Jogani 2007). The level of CO_2 produced is proportional to the amount of sodium bicarbonate ($NaHCO_3$) in the tablet. The availability of a greater quantity of CO_2 when the concentration of sodium bicarbonate ($NaHCO_3$) was raised, being caught in the produced gel to give buoyancy, can be attributed to the decrease in floating lag time of the formulations (Meka et al. 2008; Vanitha, Varma, and Ramesh2013).

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 3 May-June 2022, pp: 1379-1392 www.ijprajournal.com ISSN: 2456-4494

11. **In vitro dissolution studies** – Apparatus - USP-II, Paddle Method Dissolution Medium - 0.1 N HCl RPM – 50 Sampling intervals (hrs) - 0.5,1,2,3,4,5,6.

Temperature - 37°c + 0.5°c
As the preparation was for floating drug release given through the oral route of administration, different receptors fluids are used for evaluating the dissolution profile.

Procedure:

The release of amlodipine from floating tablets was executed by USP Dissolution Test Apparatus Type- II (Paddle method; Copley-USA). The temperature of the dissolution medium (0.1 N HCl, 900 ml) was maintained at 37±1 ˚C with a stirring rate of 50 rpm. The floating tablets were dropped inside the dissolution apparatus vessels. A 5 ml sample of the solution was withdrawn hourly, and the same number of samples was replaced with a freshdissolution medium. The obtained samples were filtered and analyzed in a triplicate using a UV-visible spectrophotometer at 366 nm and the % drug release was calculated using an equation obtained from a standard calibration curve (Arza, Gonugunta, and Veerareddy 2009; Sucharitha et al. 2013).

III. RESULTS AND DISCUSSION

Characterization of floating amlodipine tablets – PRE-COMPRESSION PARAMETERS - Pre-compression parameters play a vital role in improving the flow properties of pharmaceuticals, particularly in tablet formulation. These contain an angle of repose, bulk density, tapped density, Carr's index, and Hausner ratio.

1. **Angle of repose** - Values for the angle of repose were shown in (table 5) and found to be in the range of F1-38.65, F2-30.23, F3-36.35, F4-32.10, F5-33.56, F6-35.46 indicating good flow properties.
2. **Bulk density -** Values for the bulk density that were shown in (table 5) are found to be in the range of F1-0.46, F2-0.49, F3-0.52, F4-0.43, F5- 0.45,F6-0.48.
3. **Tapped density-** Values for the Tapped density were shown in (table 5) are found to be in the range of F1-0.52, F2-0.51, F3-0.45, F4-0.51, F5-0.46,F6-0.46.
4. **Carr's compressibility index** - Carr's Index is considered as a mensuration of powder bridge strength and stability. Thus, the values of the compressibility index range between F1-14.29. F2-12.35, F3-13.18, F4-13.26, F5-12.45, andF6-13.35 showed in (table 5) and this point outs the good flowability of the powder blend.
5. **Hausner's ratio** - Hausner's ratio was measured to determine the inter-particulate friction and consolidation. The powderblend of most formulas has Hausner's ratio F1-1.13,F2-1.04, F3-1.15, F4-1.08, F5-1.09, F6-1.11 shown in (table 5) and thus indicate good flow properties.

Table no. 5 - Pre-compression parameters

Formulations	Angle of repose	Bulk density (gm/cm2)	Tapped density (gm/cm2)	Compressibility index	Hausner's ratio
F1	38.65	0.46	0.52	14.29	1.13
F2	30.23	0.49	0.51	12.35	1.04
F3	36.35	0.52	0.45	13.18	1.15
F4	32.10	0.43	0.51	13.26	1.18
F5	33.56	0.45	0.48	12.45	1.09
F6	35.46	0.48	0.46	13.35	1.11

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 3 May-June 2022, pp: 1379-1392 www.ijprajournal.com ISSN: 2456-4494

POST-COMPRESSION PARAMETERS

1. **General appearance – table no.6**

DESCRIPTION AMLODIPINE	RESULTS
Colour	White crystalline powder
Odor	Odorless
Taste	Tasteless

2. **Size and Shape – table no.7**

RAW MATERIAL(API)	NATURE OF SAMPLE
Amlodipine	Fine powder

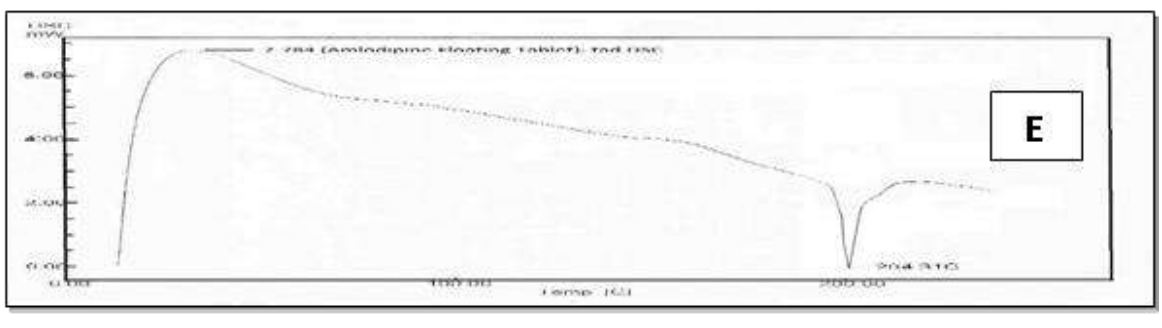
3. **Drug Content uniformity**- Values for the Drug Content uniformity wereshown in (table 8)and are found to be in the range of F_1-97.01, F_2-99.51, F_3-98.05, F_4-97.42, F_5- 96.31, F_6-97.46.
4. **Tablet thickness** - The thickness of the tablets was shown in (table 8) which was between (4.1±0.01-4.5±0.03 and)mm. From these results, it can be detected that those batches with a low concentration of polymer showed less thickness of the tablets obtained due to lower concentrations of polymer.Moreover, a higher concentration of polymers produces more thickness for less dense tablets.
5. **Hardness test** - In table 8 the hardness of the tablets was between (4.3-4.5) kg/cm2 and this confirms the best characteristics of handling for all thebatches.
6. **Friability test** - The friability of the tablets is normally performed and quite expectedly as shown in (table 8). The results of all formulas were in the range(0.84±0.04-0.93±0.02)
7. **Weight variation** - Weight is a compendial standard to assess the quality of tablets, and thus the weight variation test must indicate that all the tablets were uniform with low standard deviation values. The amlodipine floating tablets (tablet 8) indicates that the weight variation of all formulas was in the range of F_1-354±5, F_2-353±5, F_3-351±5, F_4-355±5, F_5- 352±5,F_6-353±5%.
8. **Disintegration times** - A disintegration test was conducted for all the formulations. The disintegration times of amlodipine containing HPMC K15M, and HPMCK100M as super disintegrate. The increasing order of effectiveness of super disintegrants with respective to the disintegration time in amlodipine was found to be F_1-120 sec, F_2-102 sec, F_3-110 sec, F_4-98 sec, F_5-115,F_6-109.

Table no. 8 - Drug content uniformity, Buoyancy Lag Time, Total Floating Time, Hardness, Friability, Weight variation of tablets of different formulations F1 to F6.

Formulation	Drug content uniformity	Thickness (mm)	Hardness (Kg/cm2)	Friability (%)	Weight Variation (mg)	Disintegration times (sec)
	(%)					
F_1	97.01	4.2	4.5	0.84%	354±5%	120
F_2	99.51	4.1	4.5	0.93%	353±5%	102
F_3	98.05	4.3	4.3	0.85%	351±5%	110
F_4	97.42	4.5	4.4	0.90%	355±5%	98
F_5	96.31	4.2	4.3	0.87%	352±5%	115
F_6	97.46	4.4	4.4	0.90%	353±5%	109

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 3 May-June 2022, pp: 1379-1392 www.ijprajournal.com ISSN: 2456-4494

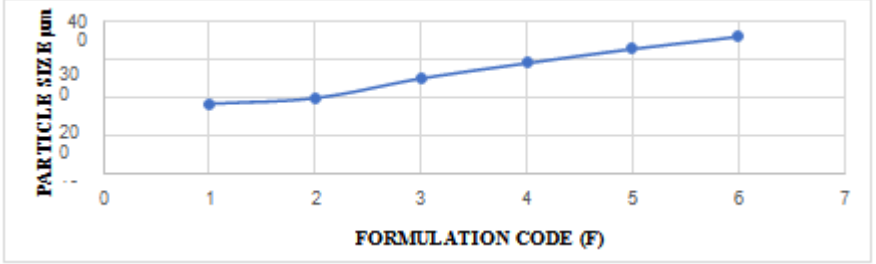
9. **Differential scanning calorimetry (DSC)** - The physical mixture showed no shift in the melting endotherm for amlodipine besylate but gavea broad endotherm indicating that there is no chemical interaction between the amlodipine besylate and mixture of polymers (HPMC K15M and K100M) nonetheless depicted some miscibility of the drug with polymers. The DSC thermogram of the optimized formula depicted a similar melting point as observed with the pureamlodipine powder. DSC thermogram of optimized formulation also shows some step changes in heat curve. These step changes are glass transition temperature which indicates the amorphous nature of other components of formulation like hydroxypropyl methylcellulose (HPMC) K15M, K100M (Choudhari et al. 2018; Damodharan et al. 2010; Govindasamy, Krishnamoorthy, and Rajappan 2013; Vora et al.2016).



10. PARTICLE SIZE AND MORPHOLOGY ANALYSIS(SEM) - keeping drug ratio constant and varied polymer ratio as the polymer concentration increases, viscosity increases, which influences the interaction between disperse phase and dispersion medium and affects the size concentration, there was an increase in relative viscosity so as an increase in mean particle size. The particle size of drug- loaded batches ranges from 183 to 358 µm. **Table No. 9 - The mean particle size of all theformulations.**

(±S.D.and no. of determinations = 3)

S.N.	FORMULATION CODE	PARTICLE SIZE µm
1	F1	183
2	F2	198
3	F3	249
4	F4	289
5	F5	326
6	F6	358



International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 3 May-June 2022, pp: 1379-1392 www.ijprajournal.com ISSN: 2456-4494

11. **Floating behavior of tablets (Buoyancy Lag Time (Sec) and Total Floating Time (hrs))** - Buoyancy lag time (BLT) and total floating time (TFT) of different formulations were noted,whereF_1BLTof133secandTFTof >12 hours, F_2 BLT of 140 sec and TFT of >20 hours, F_3 BLT of 141 sec and TFT of >24 hours, F_4 BLT of 110 sec and TFT of >16 hours, F_5 BLT of 120 sec and TFT of >18 hours, F_6 BLT of 129 sec and TFT of >22 hours About buoyancy studies results in it can be concluded that the batch containing HPMC polymers showed good buoyancy lag time (BLT) and total floating time(TFT).

The floating behavior of amlodipine tablets, including the floating lag time and total floating time, was studied and demonstrated in this study (Table 10). These floating tablets were all coated with different grades of hydrophilic polymers, as well as hydrophobic polymers, and then tested for CO_2 bubble entrapment effectiveness and matrix integrity. floating tablets (F_1-F_6) made with hydroxypropyl methylcellulose (HPMC) K15M, K100M [hydrocolloid gelling agent] absorb water and swell when they come into contact with an aqueous media (0.1 N HCl, pH 1.2), delaying medication release. In addition, the floating property of these produced tablets was tested to see how raising the hydroxypropyl methylcellulose (HPMC) K15M, and K100M concentrations affected the floating property. This polymer was discovered to be capable of maintaining matrix integrity for an extended period, with a reduction in floating lag time and a total floatation time of more than 24 hours. This might be explained by the fact that when the volume increased faster than the mass increased during swelling, the density decreased and the systems started tofloat.

Table no. 10 - Floating behavior of tablets

Formulation	Buoyancy Lag Time (Sec)	Total Floating Time (hrs)
F_1	133 sec	>12 hrs
F_2	140 sec	>20 hrs
F_3	141 sec	>24 hrs
F_4	110 sec	>16 hrs
F_5	120 sec	>18 hrs
F_6	129 sec	>22 hrs

12. In vitro dissolution studies – in vitro drug releasestudies

Dissolution parameters -

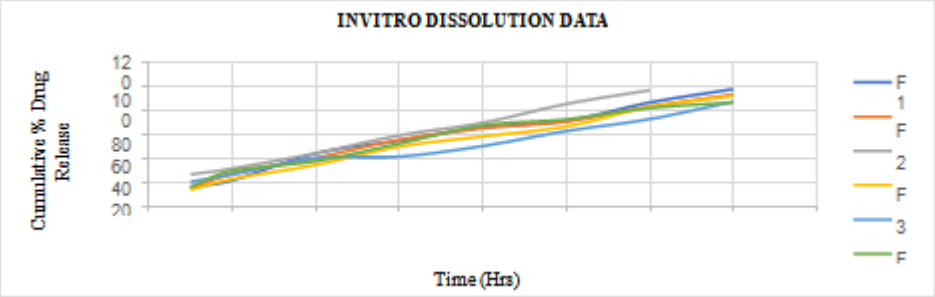
It was evident that formulations (F_1-F_6) showed rapid release within 7 h, Formulations (F_1 and F_6) were chosen to determine the effect of sodium bicarbonate ($NaHCO_3$) concentration on drug release. As shown in Table 12, raising the concentration of sodium bicarbonate had no statistically significant effect ($p>0.05$) on the drug release rate. The impact of different hydroxypropyl methylcellulose (HPMC) grades on the solubility profile of amlodipine from formulations (F_1 and F_6) was investigated, as shown in table 11. The cumulative drug release rate from hydroxypropyl methylcellulose (HPMC) K100M was substantially lower ($p0.05$) than that from HPMC K15M. This is attributed to a decrease in initial burst release, which might be related to increased swelling of the high viscosity polymer as the number of swelling increases, resulting in improved matrix integrity and a longer diffusional route length. As a result, water permeability is reduced. In terms of medication release rate, it was determined by the viscosity grade and concentration of the polymers used (El Nabarawi et al.2017).

Table no. 11 - in vitro drug release studies dissolution parameter

TIME (HRS)	CUMULATIVE % DRUG RELEASE					
	F1	F2	F3	F4	F5	F6
0.5	16.2	14.6	26.4	13.4	20.3	15.8

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 3 May-June 2022, pp: 1379-1392 www.ijprajournal.com ISSN: 2456-4494

1.0	21.5	26.9	31.3	22.6	26.4	29.4
2.0	43.9	40.1	44.1	34.3	39.8	37.5
3.0	54.6	55.3	58.9	49.5	41.3	52.1
4.0	65.7	64.8	69.5	58.1	50.1	67.3
5.0	71.1	70.5	85.2	66.4	62.6	72.4
6.0	86.4	83.0	96.6	82.6	72.6	81.8
7.0	97.6	93.1		91.7	87.1	86.4



IV. CONCLUSION –

This research found a single optimal amlodipine floating tablet formula (F6) that allowed for the production of effective tablets including a mix of hydrophilic and lipophilic polymers. Floating tablets of Amlodipine might be produced in the current study to improve stomach residence duration and hence bioavailability. Also, the administration frequency might be lowered. Amlodipine Besylate floating tablets made with the hydrophilic controlled release polymer HPMC K100M and Carbopol were found to float for the longest period and release the medicine in a gradual and controlled way. The percentage of drug release rate depends on the percentage of polymer used.
The developed system offers a simple and novel technique for Gastric Retentive Drug Delivery System. Such work can be further extended using some other controlled release polymers for drug delivery.

ACKNOWLEDGMENT - The authors would like to thank Mustansiriyah University (www.uomustansiriyah. edu iq) Baghdad-Iraq for its support in the present work. Also, the authors would like to give great thanks and appreciation for Dr. Masar Basim Mahsin Mohamed in the department of pharmaceutics, college of pharmacy Mustansiriyah University, Baghdad-Iraq,for her help and generosity.

REFERENCES

[1]. Abernethy, Darrell R., and Janice B. Schwartz. 1988. "Pharmacokinetics of Calcium Antagonists under Development." Clinical Pharmacokinetics 15(1):1–14.
[2]. Agarwal, Manyoo A., David Flatt, andRami N. Khouzam. 2018. "The Potential Detrimental Effects of Calcium Channel Blockers' Overdose and Current Available Management." Annals of Translational Medicine6(1).
[3]. Alhamdany, Anas T., and Ali Khidher Abbas. 2018. "Formulation and In Vitro Evaluationof Amlodipine Gastroretentive Floating Tablets Using a Combination of Hydrophilic and Hydrophobic Polymers." Int J App Pharm 10(6):126–34.
[4]. Anepu, Sarada, Lohithasu Duppala, and S. Sundari. 2017. "Formulation Development, Characterization, and In Vitro Evaluation of Floating Matrix Dosage Form of Tramadol Hydrochloride Using Various Polymers." Asian J Pharm Clin Res10:281–90.
[5]. Anon. n.d. "British-National-Formulary-for-Children_-the-Risk-of-Inappropriate-Paracetamol-Prescribing."
[6]. Arza, Ramji Anil Kumar, Chandra Sekhara Rao Gonugunta, and Prabhakar Reddy Veerareddy. 2009. "Formulation and Evaluation of Swellable and Floating Gastroretentive Ciprofloxacin Hydrochloride Tablets." AAPS PharmSciTech10(1):220–26.

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 3 May-June 2022, pp: 1379-1392 www.ijprajournal.com ISSN: 2456-4494

[7]. Ashok, K. P., and K. S. Damodar. 2013. "Effect of Hydrophilic and Hydrophobic Polymers and Fillers on Controlled Release Matrix Tablets of Acyclovir." Der Pharm Sinica4:143–50.
[8]. Biswas, Kausik, Ishita Chattopadhyay,Ranajit
[9]. K. Banerjee, and Uday Bandyopadhyay. 2002. "Biological Activities and Medicinal Properties of Neem (Azadirachta Indica)." Current Science82(11):1336–45.
[10]. Choudhari, Prashant Kumar, H. K. Jain, P. Sharma, and B. Srivastava. 2018. "A Novel Co-Processed Directly Compressible Release- Retarding Polymer: In Vitro, Solid State and in Vivo Evaluation." Future Journal of Pharmaceutical Sciences 4(1):29–40.
[11]. Chowdhury, M. Ehsanul H. 2012. "Preparation and Evaluation of Floating Matrix Tablets of Ranitidine Hydrochloride." The Pharma Innovation1(7).
[12]. Cifuentes, Celia, Angela Aguilar-de-Leyva, Ali R. Rajabi-Siahboomi, and Isidoro Caraballo. 2013. "Critical Points in Ethylcellulose Matrices: Influence of the Polymer, Drug and Filler Properties." Acta Pharmaceutica63(1):115–29.
[13]. Curry, Stephen H. 1983. "Novel Drug Delivery Systems, YW Chien. New York, Marcel Dekker Inc., No. of pages: 648. Price$65.00."
[14]. Damodharan, N., V. Manimaran, and B. Sravanthi. 2010. "Formulation Development and Evaluation of Delayed-Release Doxycycline Tablets." International Journalof Pharmacy and Pharmaceutical Sciences 2(Suppl 1):116–19.
[15]. El-Bagory, Ibrahim, Nahla Barakat,Mohamed Ibrahim, and Fouza El-Enzi. 2012. "Formulation and in Vitro Evaluation of Theophylline Matrix Tablets Prepared by Direct Compression: Effect of Polymer Blends." Saudi Pharmaceutical Journal 20(3):229–38.
[16]. Elliott, William J. 2012. "NICE Clinical Guideline 127: Hypertension: Clinical Management of Primary Hypertension in Adults." Yearbook of Medicine2012:336–38.
[17]. Foëx, Phil, and J. W. Sear. 2004. "Hypertension: Pathophysiology and Treatment." Continuing Education in Anaesthesia Critical Care & Pain4(3):71–75.
[18]. Govindasamy, GOPI, KANNAN Krishnamoorthy, and MANAVALAN Rajappan. 2013. "Selection of Excipients for Nanoparticles Formulations of Nateglinide through Drug-Excipients Compatibility Study." International Journal of Pharmacy and Pharmaceutical Sciences 5(2):371–77.
[19]. Gradman, Alan H., Jan N. Basile, Barry L. Carter, George L. Bakris, and American Society of Hypertension Writing Group. 2010. "Combination Therapy in Hypertension." Journal of the American Society of Hypertension4(2):90–98.
[20]. Gupta, M. M. 2013. "Formulation Development And Evaluation Of Immediate Release Tablet of Anti Hypertensive Drug Olmesartan Medoxomile." The Pharma Innovation 2(3, PartA):68.
[21]. Hamid, A., and M. Merchant. 2006. "Harris Shoiab, Jaweria Tazeen. Once Daily Tablet Formulation and In Vitro Release Evaluation of Cefpodoxime Using HPMC." AAPS Pharm Sci Tech7(3).
[22]. Hermida, Ramón C., Diana E. Ayala, Artemio Mojón, and José R. Fernández. 2008. "Chronotherapy with Nifedipine GITS in Hypertensive Patients: Improved Efficacy and Safety with Bedtime Dosing." American Journal of Hypertension21(8):948–54.
[23]. Jagdale, Swati C., Amit J. Agavekar, Sudhir V Pandya, Bhanudas S. Kuchekar, and Aniruddha R. Chabukswar.2009."Formulation and Evaluation of Gastroretentive Drug Delivery System of PropranololHydrochloride." AAPS PharmSciTech 10(3):1071–79.
[24]. Julius, Stevo. 1988. "Amlodipine in Hypertension: An Overview of the Clinical Dossier." Journal of Cardiovascular Pharmacology12:S27-33.
[25]. Meka, Lingam, Bhaskar Kesavan, Krishna Mohan Chinnala, Venkateswarlu Vobalaboina, and Madhusudan Rao Yamani. 2008. "Preparation of a Matrix Type Multiple-Unit Gastro Retentive Floating Drug Delivery System for Captopril Based on Gas Formation Technique: In Vitro Evaluation." AAPS PharmSciTech9(2):612–19.
[26]. El Nabarawi, Mohamed A., Mahmoud H. Terima, Rehab A. Abd El-Monem, Nagla A. El Nabarawy, and Dalia A. Gaber. 2017. "Formulation, Release Characteristics, and Bioavailability Study of Gastroretentive Floating Matrix Tablet and Floating Raft

System of Mebeverine HCl." Drug Design, Development and Therapy 11:1081.
[27]. Oparil,Suzanne,M.AminZaman,andDavid Calhoun. 2003. "Pathogenesis of Hypertension." Annals of Internal Medicine 139(9):761–76.
[28]. Palma-Gámiz, José L. 1997. "High Blood Pressure and Calcium Antagonism." Cardiology 88(Suppl.1):39–46.
[29]. Pare, A., S. K. Yadav, and U. K. Patil. 2008. "Formulation and Evaluation of Effervescent Floating Tablet of Amlodipine Besylate." Research Journal of Pharmacy and Technology1(4):526–30.
[30]. Patel, D. M., N. M. Patel, and P. D. Jogani. 2007. "Formulation and Optimization of Carbamazepine Floating Tablets." Indian Journal of Pharmaceutical Sciences69(6):763.
[31]. Pawar, Harshal Ashok, and Rachana Dhavale. 2014. "Development and Evaluation of Gastroretentive Floating Tablets of an Antidepressant Drug by Thermoplastic Granulation Technique." Beni-Suef University Journal of Basic and Applied Sciences 3(2):122–32.
[32]. Pawar, Harshal Ashok, Pooja Ramchandra Gharat, Rachana Vivek Dhavale, Pooja Rasiklal Joshi, and Pushpita Pankajkumar Rakshit. 2013. "Development and Evaluation of Gastroretentive Floating Tablets of an Antihypertensive Drug Using Hydrogenated Cottonseed Oil." International Scholarly Research Notices 2013.
[33]. Rahim, Safwan Abdel, Paul A. Carter, and Amal Ali Elkordy. 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 9:1843.
[34]. Reddy,K.SaiMadhav,LaxmidharSahoo,Dr.G. Kamalakar Reddy, and L. Vamsi Krishna. 2011. "Formulation and Evaluation of Immediate Release Tablets of Linezolid." International Journal of Pharmaceutical & Biological Archives 2(4):1230–35.
[35]. Shahi, Sadhana R., Shivram B. Shinde, Nityanand S. Zadbuke, and Abhay N. Padalkar. 2014. "Formulation Development and Evaluation of Floating Matrix Tablet of Verapamil HCl." Asian Journal of Pharmaceutics (AJP): Free Full-Text Articles from Asian J Pharm7(1).
[36]. Sheraz, Muhammad Ali, Syed Furqan Ahsan, Marium Fatima Khan, Sofia Ahmed, and Iqbal Ahmad. 2016. "Formulations of Amlodipine: A Review." Journal of Pharmaceutics2016.
[37]. Singh, Brahma N., and Kwon H. Kim. 2000. "Floating Drug Delivery Systems: An Approach to Oral Controlled Drug Delivery via Gastric Retention." Journal of Controlled Release 63(3):235–59.
[38]. Sinha, V. R., M. K. Agrawal, and R. Kumria. 2005. "Influence of Formulation and Excipient Variables on the Pellet Properties Prepared by Extrusion Spheronization." Current Drug Delivery 2(1):1–8.
[39]. Sood, Richa, M. S. Rathore, A. Sharma, Richa Thakur, J. Chaudhari, and V. Soni. 2012. "Immediate Release Antihypertensive Valsartan Oral Tablet: A Review." Journal of Scientific Research in Pharmacy May 1(2):20– 26.
[40]. St-Onge, M., P. A. Dubé, S. Gosselin, C. Guimont, J. Godwin, P. M. Archambault, J. M. Chauny, A. J. Frenette, M. Darveau, and N. Le Sage. 2014. "Treatment for Calcium Channel Blocker Poisoning: A Systematic Review." Clinical Toxicology 52(9):926–44.
[41]. Sucharitha, M., A. N. Devi, V. P. Priya, and Sharma J. V. C. Shyamala. 2013. "Formulation and Evaluation of Gastroretentive Floating Tablets of Valsartan." World J Pharm Pharm Sci3:689–702.
[42]. Sungthongjeen, Srisagul, Pornsak Sriamornsak, and Satit Puttipipatkhachorn. 2011. "Design of Floating HPMC Matrix Tablets: Effect of Formulation Variables on Floating Properties and Drug Release." Pp. 1140–43 in Advanced Materials Research. Vol. 311. Trans TechPubl.
[43]. Triggle, David J. 2007. "Calcium Channel Antagonists: Clinical Uses—Past, Present, and Future." Biochemical Pharmacology 74(1):1– 9.
[44]. Tripathi, K. D. 2003. "Essentials of Medical Pharmacology, Jaypee Brothers." Medical Publishers (P) Ltd, New Delhi, Edition 5:93–94.
[45]. Vanitha, Kondi, Mohan Varma, and Alluri Ramesh. 2013. "Floating Tablets of Hydralazine Hydrochloride: Optimization and Evaluation." Brazilian Journal of Pharmaceutical Sciences 49(4):811–19.
[46]. Vora, Chintan, Riddhish Patadia, KaranMittal, and Rajashree Mashru. 2016.

"Preparation and Characterization of Dipyridamole Solid Dispersions for Stabilization of Supersaturation: Effect of Precipitation Inhibitors Type and Molecular Weight." Pharmaceutical Development and Technology 21(7):847–55.

[47]. De Vries, Rob J. M., Dirk J. Van Veldhuisen, and Peter H. J. M. Dunselman. 2000. "Efficacy and Safety of Calcium Channel Blockers in Heart Failure: Focus on Recent Trials with Second-GenerationDihydropyridines." American Heart Journal 139(2):185–94.

[48]. Vukadinovic, Davor, Sean S. Scholz, Franz H. Messerli, Michael A. Weber, Bryan Williams, Michael Boehm, and Felix Mahfoud. 2019. "Peripheral Edema and Headache Associated with Amlodipine Treatment: A Meta-Analysis of Randomized, Placebo-Controlled Trials." Journal of Hypertension37(10):2093–2103.