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FORMULATION, DEVELOPMENT AND EVALUATION OF FUROSEMIDE AND AMLODIPINE ORODISPERSIBLE TABLETS AS NOVEL DELIVERY SYSTEMS

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ABSTACT

The objective of the present study was to prepare Furosemide and Amlodipine as Orodispersible tablets drug delivery systems. Orodispersible tablets dissolve rapidly and show higher bioavailability than conventional tablets. Furosemide and Amlodipine was selected as a model for preparation of Orodispersible Tablets by direct compression technique. Amlodipine is a long-acting calcium channel blocker (dihydropyridine) used as an anti-hypertensive and in the treatment of angina. Amlodipine is one of the calcium channel blockers that works primarily on arterial muscle and it acts by relaxing smooth muscle in the arterial wall, decreasing peripheral resistance and hence reducing blood pressure; in angina it increases blood flow to the heart muscle. Furosemide is a loop diuretic commonly used in adults, infants and children for the treatment of edematous states associated with congestive heart failure, cirrhosis of the liver and renal disease. Oral Furosemide may be used in adults for the treatment of hypertension alone or in combination with other antihypertensive agents; however, they are slow to produce the desirable effect. Therefore, to decrease the patient time in suffering of these symptoms, Orodispersible drug-delivery system significantly increased patient acceptance by virtue of rapid disintegration, self-administration without water and finally improved patient compliance. Tablets were prepared by direct compression method using crospovidone and sodium starch glycolate as superdisintegrants. The tablets were evaluated for weight variation, thickness, diameter, hardness, friability, time, *in-vitro* disintegration time, assay HPLC method and *in-vitro* dissolution study. Hardness and friability data indicated good mechanical strength of tablets. The results of *in-vitro* disintegration time of F4 and F2 was found to be 9 and 2 seconds and the drug release 90.72% and 76.51% at 5 minutes respectively indicated that the tablets dispersed rapidly in the mouth. It was concluded that F4 and F2 are the best formulations of Furosemide and Amlodipine Orodispersible Tablets ODTs drug delivery systems in order to increase onset of action and bioavailability of drug.

KEYWORDS: Furosemide, Amlodipine, Orodispersible tablets, Superdisintegrants, Drug delivery systems.

INTRODUCTION

Oral drug delivery systems[1-150]

Most of the oral pharmaceutical dosage forms like conventional tablets and capsules are formulated to be swallowed or chewed. Elderly people and children sometimes have difficulties in swallowing these dosage forms. Such problem is more serious for bedridden patients. This problem is also applicable to active working or travelling people who do not have ready access to water. Recent advances in novel drug delivery system aims to provide rational drug therapy by enhanced safety and efficacy of drug molecule by formulating a convenient dosage form for administration and also by ensuring better patient compliance.

Oral drug delivery has been known as the most widely used route of drug administration when compared to all the other routes that have been explored for delivery of different dosage forms to systemic circulation. The reason for such popularity of oral route may be attributed to its ease of administration. Recent advances in novel drug delivery systems (NDDS) aim at formulating a convenient dosage form for administration and to

achieve better patient compliance to enhance safety and efficacy of drug molecules.

An oral fast dissolving drug delivery system is a novel tablet dosage form, which dissolves or disintegrates in the oral cavity with a good taste and flavor increasing the acceptability of bitter drugs without the need of water or chewing and hence called melt in mouth tablets or Orodispersible or rapid disintegrating or quick dissolving tablets. The drugs may be absorbed from mouth, pharynx or esophagus while the saliva passes down into stomach. Advantages of the fast-dissolving tablets include rapid onset of action, ease of swallowing without the aid of water, enhanced dissolution rate, increased gastric absorption, minimized first pass metabolism, improved oral bioavailability and improved patient compliance. ODTs formulation combines the advantages of both conventional tablets and liquid formulations.

Solid dosage forms are popular because of low cost, ease of administration, accurate dosage self-medication, pain avoidance, and the most importantly the patient compliance. The most prevalent solid dosage forms are being tablets and capsules. One essential downside of such dosage forms is Dysphagia (Trouble in gulping) is basic among all age gatherings. Normal grumblings about the trouble in gulping tablets are size, surface, and taste of tablets. Geriatric and pediatric patients and voyaging patients, who might not have prepared access to water, are most needing simple gulping dosage forms. To satisfy these medicinal needs, pharmaceutical technologists have built up a novel oral dosage form known as Orodispersible tablets (ODTs) which disintegrate quickly in salivation, normally inside only seconds, without the need to take water.

Through the few Ten years, there has been a strong request for more rapid, patient-friendly and convenient dosage forms of drug. Though, oral routes of drug administration have got the widest acceptance comparing to the other routs of administration. Moreover, improved patient compliance is demanded in this modern era. Therefore, demand for the new technologies is also increasing. To develop a chemical entity, there is need of lot of money, hard work and sufficient time. So, focus is rather being laid on the development of new drug delivery systems for already existing medication, with enhanced efficacy and bioavailability, thus reducing the dose and dosing frequency to minimize the side effects. It is always the desire of a scientist or a dosage form designer to augment the safety of a drug molecule while maintaining its therapeutic efficacy. Recent advances in Novel Drug Delivery Systems (NDDS) wish for the same by formulating a dosage form, which is easy to be administered so as to achieve better patient compliance. For most therapeutic agents used to produce systemic effects, the oral route still represents the preferred way of drug administration, owing to its several advantages and high patient compliance compared to many other routes.

However, patients especially elder ones find tablets and capsules are difficult to be swallowing. It is estimated that 35% of the population is affected by this problem which results in a high incidence of non-compliance and ineffective therapy. The difficulty is experienced in particular by pediatric and geriatric patients, but it also applies to people who are ill in bed and to those active working patients who are busy or traveling, especially those who have no access to water and also in following conditions like: Parkinsonism, Motion sickness, Unconsciousness and Mentally disabled persons. Accordingly, to fulfil these medical needs the pharmaceutical technologists have developed a novel type of dosage form for oral administration, the Orodispersible (ODTS), tablets that disintegrate and dissolve rapidly in saliva without water. Sufficiently high aqueous solubility is crucial for their success, however. This requirement becomes increasingly problematic with the increasing number of poorly water-soluble drugs emerging onto the market.

hypertension is an important problem that requires chronic treatment. Angiotensin-converting enzyme (ACE) inhibitors were primarily considered as antihypertensive drugs which are able to reduce significantly high blood pressures in hypertensive patients. Calcium channel blockers were initially considered for treatment of angina pectoris and for the treatment of vasospastic angina. These drugs are able to markedly reduce vascular resistance and for that reason they were extensively studied in the field of hypertension. ACE inhibitors and calcium channel blocker drugs are widely used for the treatment of many cardiovascular conditions including mild to moderate hypertension and heart failure, either alone or in combination with other drugs.

The main purpose of this study was to formulate and develop an ODTS of a combined product. To produce a drug of rapid onset of action with relative disintegration time, to improve bioavailability, increase absorption and enhancing dissolution rate, to formulate a dosage form that can be used ODTs in emergency to reduce hypertension and maintains diuretic effect, to increase safety by diminishing the difficulties of swallowing, risk of chocking or suffocation, to reduce drug multiple intakes, to serve in reducing economical cost issue and exploit the chances for better efficacy and prevent development of drug resistance.

Furosemide [4-chloro-N-furfuryl-5-sulphamoylanthranilic acid], is a loop diuretic commonly used in adults, infants and children for the treatment of edematous states associated with congestive heart failure, cirrhosis of the liver and renal disease. Oral Furosemide may be used in adults for the treatment of hypertension alone or in combination with other antihypertensive agents.

Amlodipine (as besylate, mesylate or maleate) [(RS)-3-ethyl 5-methyl 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl) - 6-methyl - 1,4 – dihydropyridine -3 ,5-dicarboxylate], is a long-acting calcium channel blocker (dihydropyridine) used as an anti-hypertensive and in the treatment of angina. Amlodipine is one of the calcium channel blockers that works primarily on arterial muscle and it acts by relaxing smooth muscle in the arterial wall, decreasing peripheral resistance and hence reducing blood pressure; in angina it increases blood flow to the heart muscle.

The oral route of drug administration is the most important method of administering drugs for systemic effects. Of drugs that are administered orally, solid oral dosage form represents the preferred class of products. Solid medicaments may be administered orally as powders, pills, cachets, capsules or tablets. These dosage forms contain a quantity of drug which is given as a single unit and they are known as solid unit dosage forms. Tablets represent unit dosage form in which one usual dose of the drug has been accurately placed. Tablets may be defined as solid pharmaceutical dosage forms containing drug substance with or without suitable diluents and have been traditionally prepared either by compression or molding methods. Frequently, tablets are discoid in shape; they are also round, oval, oblong, cylindrical or triangular. They differ greatly in size and weight depending on the amount of drug substance present and intended method of administration. Tablets are obtained by compression of uniform volumes of powders or granules by applying high pressure and using punches and dies. The particles to be compressed consist of one or more medicaments, with or without auxiliary substance such as diluents, binders, and disintegration agents, lubricant, glide ants and substances capable of modifying the behavior of the medicaments in the digestive tracts. Such substances must be innocuous and therapeutically inert in the quantities present.

The aim of the present study was to investigate the use of superdisintegrant to formulation, development and evaluation of Furosemide and Amlodipine besylate ODTs with the intended application as ODTs.

MATERIALS AND METHODS

Furosemide and Amlodipine Besylate were obtained as a gift from (Biopharm Pharmaceutical Industry Company-Yemen). While Crospovidone**,** Microcrystalline Cellulose, Sodium Starch Glycolate**,** Magnesium Stearate**,** Sodium Lauryl Sulfate (SLS)**,** Aspartame and other materials were obtained as a gift from (Shaphaco Pharmaceutical Industry Company-Yemen).

The equipment's used as shown in Table 1.

Table 1: The Equipment's Used.

No	Equipment's
1	Fourier Transform Infrared Spectrophotometer (IR. Thermoscientific Nicolet is 10)
2	UV/VIS Spectrophotometer (uv jasco 2016) No: Qc. cp-057
3	pH Meter HI 2216 pH/ ORP/ISE Meter
4	Ultra-sonic
5	Electronic Balance Sartorius No: Qc-Cp, 059
6	Hardness Tester Rimek- India. No: cp.010.
7	Disintegration Tester (disintegration tester -bj-3)
8	HPLC 2020
9	Dissolution Tester (Rc- 80C) No: Qc-cp-071
10	Tablet Machine Rotary tablets press machine Zp-7
11	Friability Tester (Cjy-300D Tablets friability tester)
12	Thickness Tester Vernier (Stainless hardened)
13	Oven (Incubator) Accelerate Stability Study Champer

Formulation and Evaluation of Furosemide and Amlodipine Formulations ODTs[50-190]

Preparation of Furosemide and Amlodipine Formulations ODTs

Formulations (F1-F6) each tablet containing 20 mg Furosemide and 5 mg Amlodipine were prepared by direct compression method using the ingredients as shown in Table 1. Six formulations were prepared using pure drug Furosemide and Amlodipine and two superdisintergrants namely crospovidone and sodium starch glycolate. Mixing was done by using geometric mixing, in where all excipients accurately weighed then all of them except magnesium striate were blended with specified quantity of Furosemide and Amlodipine for 15minutes, whereas the other excipients were blended for 5 minutes and added to the former excipients. Then all formulations were passed through sieve # 18 for particle size uniformity. This method of ordering mixing of excipients with Furosemide and Amlodipine in first sex formulations. Then each mixture has compressed directly into tablets using rotary tablet compression machine of punch size 6.25mm (7mm) to prepare tablets each weighing 150mg after testing powder properties that will be shown in Preformulation tests in early research as shown in Table 2.

Table 2: Composition of Furosemide and Amlodipine Formulations ODTs.

Ingredients	Quantity per tablet					
	Formulation code					
	F1	F2	F3	F4	F5	F6
Amlodipine	5	5	5	5	5	5
Furosemide	20	20	20	20	20	20
Microcrystalline Cellulose	110.4	111	110	111	110	110.4
Sodium Starch Glycolate				8	9	8.5
Crospovidone	8.6	9	8			
Magnesium Stearate	1.5	1.5	1.5	1.5	1.5	1.5
Sodium Lauryl Sulfate SLS	1.5	1.5	1.5	1.5	1.5	1.5
Aspartame	3	3	3	3	3	3

Evaluation of Furosemide and Amlodipine orodispersible tablets

Weight variation

The weight variation test would be satisfactory method of determining the drug content uniformity. Twenty tablets randomly were taken from each batch and weighted individually, calculating the average weight, and comparing the individual tablet weights to the average. The average weight of one tablet was calculated.

Diameter test

The diameter test one of tests which used for determination of the tablets size, it is done by taking five tablets from each batch randomly. Diameter may obtain by using suitable micrometer.

Thickness test

The thickness test of five tablets were picked from each batch randomly and thickness was measured individually using "Vernier- caliper" (Electronic Digital Caliper). It is expressed in millimeter and average was calculated.

Hardness test

The hardness test or tablet crushing strength. The force required to break a tablet in a diametric compression was measured using digital tablet hardness tester. It is expressed in kg/cm^2. Five tablets were randomly selected from each batch and hardness of tablets was determined by using digital hardness tester. The mean values and standard deviation for each batch were calculated.

Friability test

The friability test is performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap or break. Roche friabilator was used for the purpose. Pre-weighed sample of five tablets from each batch were placed in the friabilator, which was then operated for 100 revolutions. After 100 revolutions the tablets were dusted and reweighed. Compressed tablets should not lose more than 1% of their weighed.

***In-vitro* disintegration time**

The *in-vitro* disintegration time was determined using disintegration test apparatus. A tablet was placed in each of the six tubes of the apparatus and one disc was added to each tube. The time in seconds taken for complete disintegration of the tablet with no palatable mass remaining in the apparatus was measured in seconds.

Assay of Furosemide and Amlodipine ODTs by HPLC Method

Chromatographic conditions

- Column: Reversed phase C18 column.
- Mobile phase: Consisted of water (15 mM Ortho-phosphoric acid) and acetonitrile (50:50 v/v).
- Buffer: Ortho-phosphoric acid (min. 85%).
- Flow rate: 1 ml/minute.
- Injection volume: 10µ.
- Wavelength: 238nm.
- Temperature: 37°C.

Preparation of phosphate solution
Dissolve 4.1g of Ortho-phosphoric acid (min. 85%).in about 900ml of water in a 1000 ml volumetric flask, and adjust with phosphoric acid to a pH of 2.0. Dilute with water to volume, and mix.

Preparation of diluent solution
Prepare a mixture of water and menthol (4:1).

Preparation of standard solution
Dissolve an accurately weighed quantity of USP 20mg of Furosemide and 5mg of Amlodipine. transferred into a 100 mL calibrated flask, diluted with methanol, stirred for about 10 min and then completed to volume with the same solution into a 100 mL then take 1ml from this solution and diluted with methanol into a 10mL.

Preparation of sample solution
5 tablets containing individually 20mg of Furosemide and 5mg of Amlodipine were finely powdered separately. An accurate weight of the powder equivalent to one tablet content was weighed, transferred into a 100 mL calibrated flask, diluted with methanol, stirred for about 10 min and then completed to volume with the same solution into a 100 mL then take 1ml from this solution and diluted with methanol into a 10 ml after filtration, the methods were established by triplicate injections of solutions containing Furosemide and Amlodipine.

Sample injection procedure
Separately inject equal volumes (about 10 µl) of the Standard preparation and the assay preparation into the chromatograph, record the chromatograms, and measure the area responses for the major peaks.

Calculate the quantity, in mg, of Furosemide and Amlodipine in each tablet taken by formula: (L/D) C (ru/rs) L:is labeled quantity, in mg of Furosemide and Amlodipine in each tablet. D: is concentration, in mg/ml of Furosemide and Amlodipine of sample preparation. C: is the concentration calculate on the anhydrous basis of USP

Furosemide and Amlodipine in standard preparation. ru and rs: are the peak area responses obtained from standards and sample preparation.

***In-vitro* Dissolution Studies of Furosemide and Amlodipine ODTs**
The *in-vitro* drug release was determined by estimating the dissolution profile. USP I Basket apparatus was used and Basket was allowed to rotate at 50 rpm. Phosphate buffer (pH 6.8) 900 ml was used as a dissolution medium at 37±0.5°C temperature. Determination of amount of drug dissolved form tablets was carried by UV Spectrophotometer. In this test, six tablets from each batch were used for the studies. At specified time intervals (5, 10, 30), 5 ml of samples were collected and immediately replaced with an equal volume of fresh medium. Samples were analyzed by using UV Spectrophotometer at 276nm and 238nm respectively using phosphate buffer as blank.

RESULTS AND DISCUSSION

Evaluation of Furosemide and Amlodipine Orodispersible Tablets

Table 3: Results of Post Compression Weight Variation (mg) ODTs.

NO	Weight Variation (mg)					
	F1	F2	F3	F4	F5	F6
1	188	147	165	150	155	147
2	160	159	155	148	152	158
3	185	146	150	147	149	147
4	148	141	149	167	147	147
5	155	144	147	145	148	149
6	154	154	148	146	151	150
7	127	143	152	162	146	155
8	143	158	154	148	158	148
9	160	147	147	151	150	152
10	131	147	148	149	148	154
Total	1551	1486	1514	1513	1513	1500
Average weight(X)	155.1	148.6	151.4	151.3	151.3	150
SD=X*7.5%	11.6	11.1	11.3	11.34	11.34	11.25
Lower Range	143.5	137.5	140.1	140	140	138.75
Higher Range	166.7	159.7	162.7	162.6	162.6	161.25

All formulations of and Furosemide and Amlodipine ODTs passed the weight variation test since the values are within the acceptable variation limit of the tablet as shown in Table 3.

Table 4: Evaluation of Post Compression Parameters of Furosemide and Amlodipine Formulations ODTs.

Formulation Code	Average Weight(mg)±S.D	Thickness (mm)	Diameter (mm) ± S.D	Friability %	Hardness Kg/cm^2	*In-Vitro* Disintegration (Sec)Time
F1	155±0.6	5.3±0.04	8.19±0.41	0.66±0.01	10±0.15	3
F2	148±0.7	5.4±0.04	8.17±0.41	0.65±0.02	9.2±0.12	2
F3	151±0.5	5.3±0.02	8.41±0.42	1.10±0.03	10±0.15	4
F4	151±0.6	5.4±0.04	8.45±0.42	0.38±0.03	9.8±0.14	9
F5	151±0.7	5.3±0.04	8.41±0.42	0.07±0.01	11±0.25	5
F6	150±0.6	5.3±0.02	8.42±0.42	0.47±0.03	12±0.30	7

As shown in Table 4, the hardness of the tablets for all formulations was measured and the values were found in the range between 9.2 to 12 kg/cm^2. The prepared tablets possessed good mechanical strength with sufficient hardness. The thickness of the tablets was measured and were found in the range between 5.3± 0.149 mm to 5.4±0.1755 mm. All the formulations possessed uniform thickness and in the accepted range. The diameter of the tablets was measured and were found in the range between 8.17± 0.41 mm to 8.45±0.42 mm. All the formulations possessed uniform diameter and in the accepted range. Similarly, percentage friability values of the prepared Furosemide and Amlodipine ODTs showed less than 1% weight loss that is highly within the acceptable limit except F3 it showed more than 1% weight loss (present capping). Disintegration time was determined and the best disintegration time taken for the formulation F2 was found to be 2 seconds. The order of disintegration time of formulations with respect to super disintegrant was found to be crospovidone more effect than sodium starch glycolate. As the concentration of superdisintegrants in the formulations increases, the time taken for disintegration decrease.

Assay of Furosemide and Amlodipine by HPLC Method

The assay was carried out by HPLC method as per the procedure given in methods. The HPLC chromatogram of Furosemide and Amlodipine standard and sample formulations were shown in Figures (1-6) and Tables (5-10).

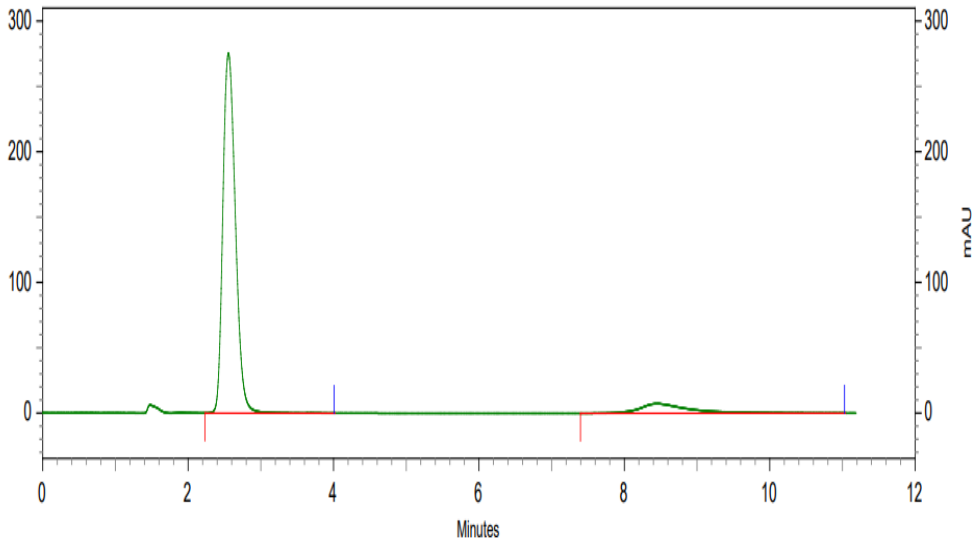

Fig. 1: HPLC Chromatogram of STD-01.

Table 5: Assay of Furosemide and Amlodipine of STD-01.

Name of drug	Retention Time	Area	Height	Theoretical Plates (USP)	Resolution (USP)	Asymmetry
Furosemide	8.235	1942237	37344	620	6.83162	2.42575
Amlodipine	2.658	24013685	2084951	1176	0.00000	1.02847
Total	10.893	25955922	2122295	1796	6.83162	1.02847

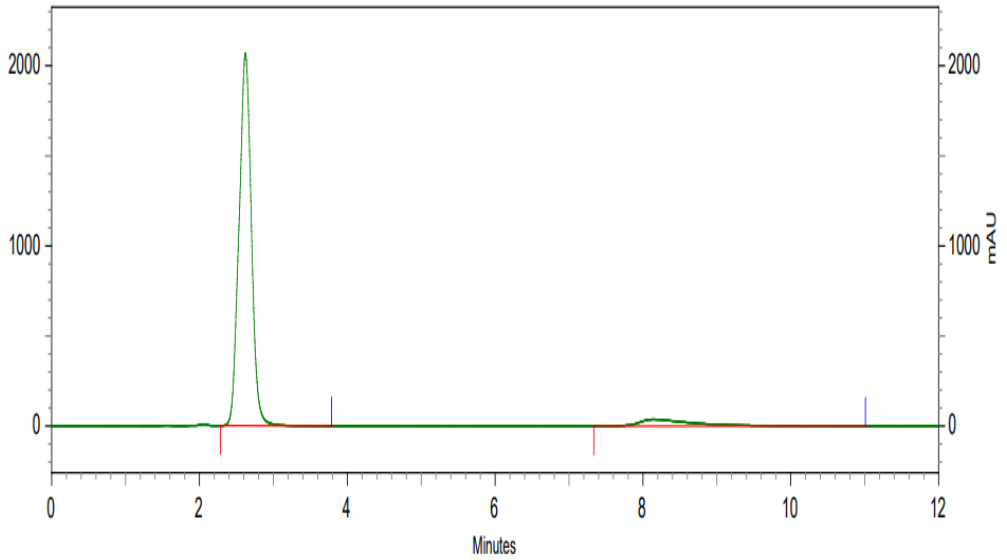

Fig. 2: HPLC Chromatogram of STD-02.

Table 6: Assay of Furosemide and Amlodipine of STD-02.

Name of drug	Retention Time	Area	Height	Theoretical Plates (USP)	Resolution (USP)	Asymmetry
Furosemide	8.143	1907267	37356	645	6.92314	2.36987
Amlodipine	2.622	23947768	2065554	1128	0.00000	1.02283
Total		25855035	2102910			

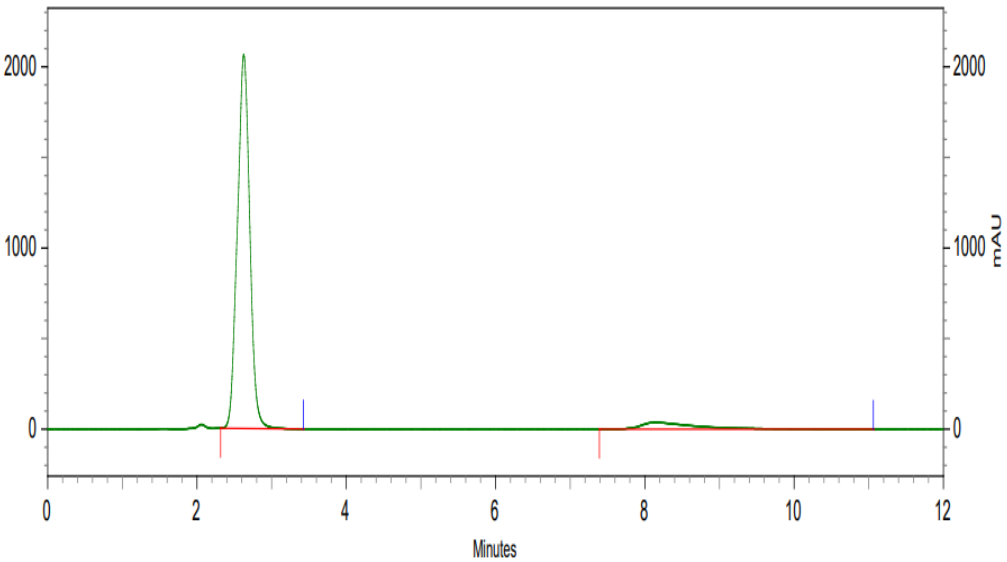

Fig. 3: HPLC Chromatogram of STD-03.

Table 7: Assay of Furosemide and Amlodipine of STD-03.

Name of drug	Retention Time	Area	Height	Theoretical Plates (USP)	Resolution (USP)	Asymmetry
Furosemide	8.138	1912228	37314	632	6.85712	2.40736
Amlodipine	2.627	23783809	2061908	1133	0.00000	1.02434
Total	10.765	25696037	2099222	1765	6.85712	4.4317

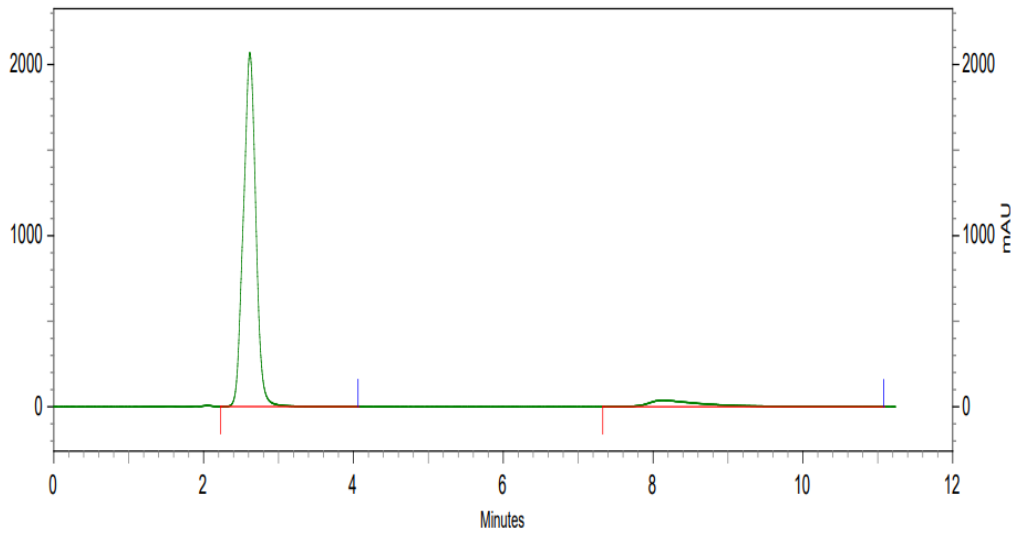

Fig. 4: HPLC Chromatogram of STD-04.

Table 8: Assay of Furosemide and Amlodipine of STD-04.

Name of drug	Retention Time	Area	Height	Theoretical Plates (USP)	Resolution (USP)	Asymmetry
Furosemide	8.127	1920093	37569	641	6.90632	2.42528
Amlodipine	2.617	23879924	2066972	1129	0.00000	1.02005
Total	10.744	25800017	2104541	1770	6.90632	3.44533

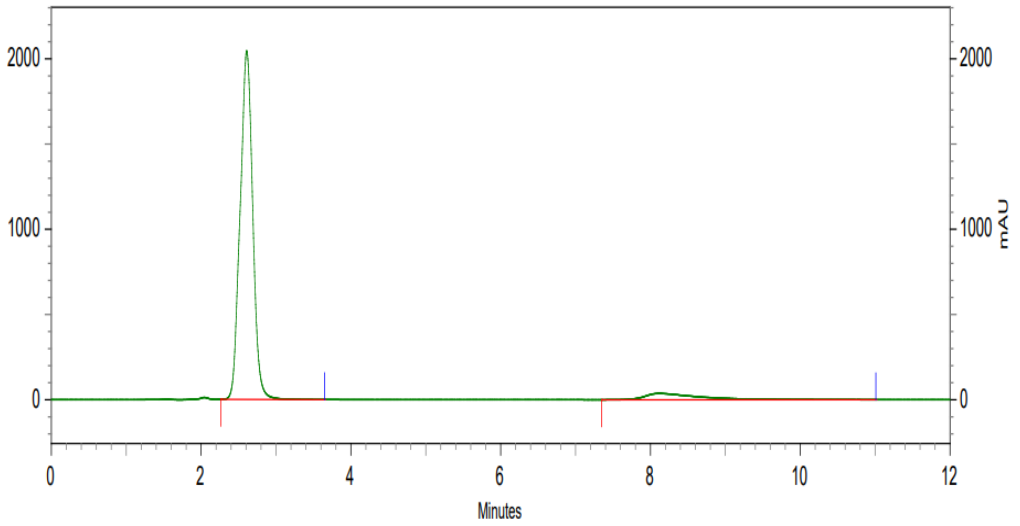

Fig. 5: HPLC Chromatogram of STD-05.

Table 9: Assay of Furosemide and Amlodipine of STD-05.

Name of drug	Retention Time	Area	Height	Theoretical Plates (USP)	Resolution (USP)	Asymmetry
Furosemide	8.118	1898961	37275	643	6.89175	2.36597
Amlodipine	2.608	23906202	2044896	1076	0.00000	1.02209
Total	10.726	25805163	2082171	1719	6.89175	3.38806

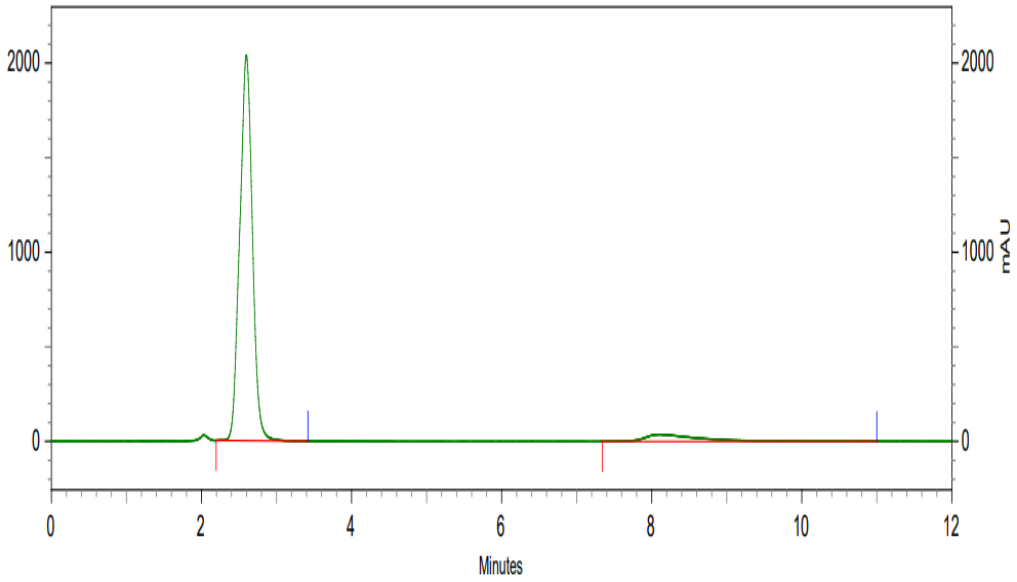

Figure 6: HPLC Chromatogram of STD-06.

Table 10: Assay of Furosemide and Amlodipine of STD-06.

Name of drug	Retention Time	Area	Height	Theoretical Plates (USP)	Resolution (USP)	Asymmetry
Furosemide	8.105	1906727	37260	630	6.83124	2.39035
Amlodipine	2.598	23912757	2038230	1052	0.00000	1.01777
Total	10.703	25819484	2075490	1682	6.83124	3.40812

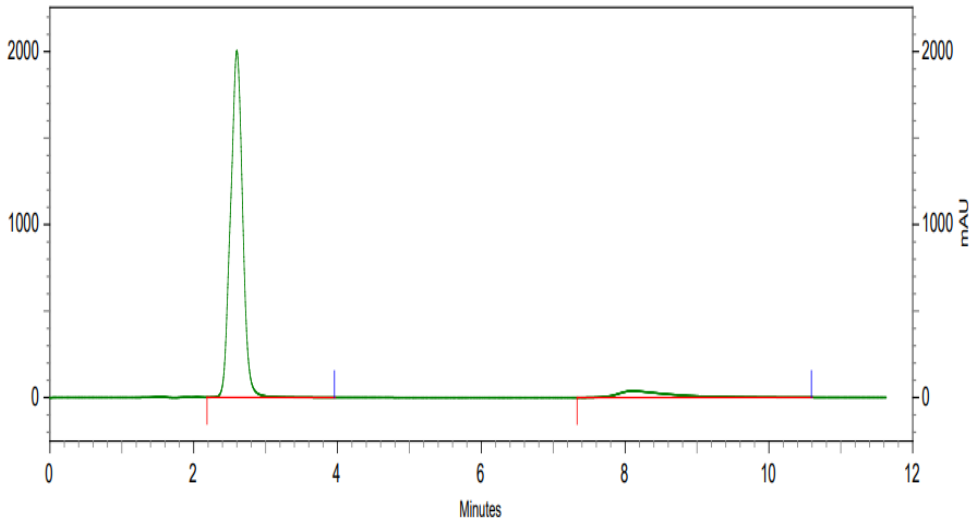

Fig. 7: HPLC Chromatogram of Formulation F1.

Table 11: Assay of Furosemide and Amlodipine of Formulation F1.

Name of drug	Retention Time	Area	Height	Theoretical Plates (USP)	Resolution (USP)	Asymmetry
Furosemide	8.105	1940799	38088	604	6.72989	2.20979
Amlodipine	2.600	23394872	2004479	1080	0.00000	1.01657
Total	10.705	25335671	2042567	1684	6.72989	3.22636

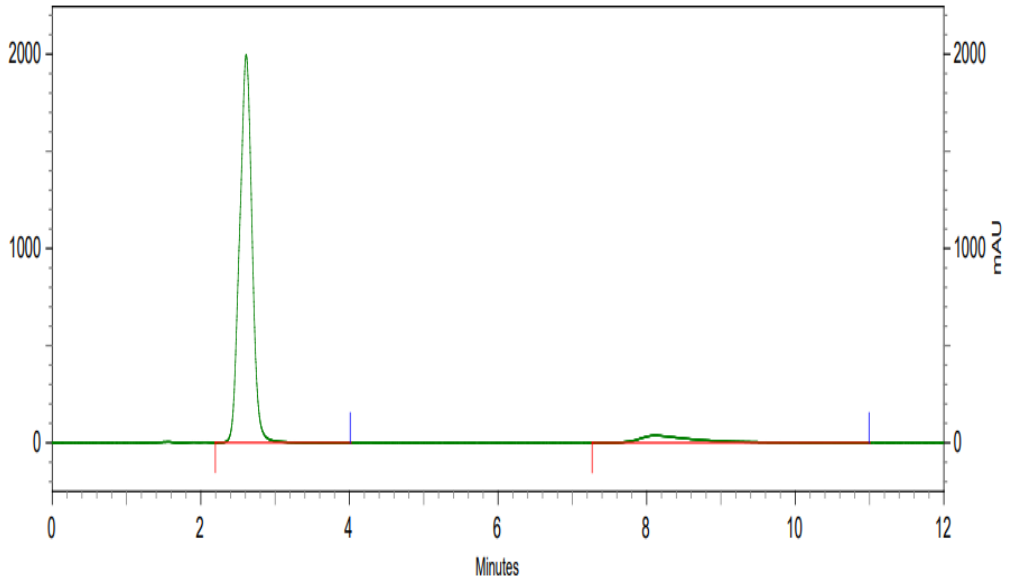

Fig. 8: HPLC Chromatogram of Formulation F2.

Table 12: Assay of Furosemide and Amlodipine of Formulation F2.

Name of drug	Retention Time	Area	Height	Theoretical Plates (USP)	Resolution (USP)	Asymmetry
Furosemide	8.113	1913176	37053	614	6.76682	2.25851
Amlodipine	2.603	23491048	1999975	1067	0.00000	1.01415
Total	10.716	25404224	2037028	1681	6.76682	3.27266

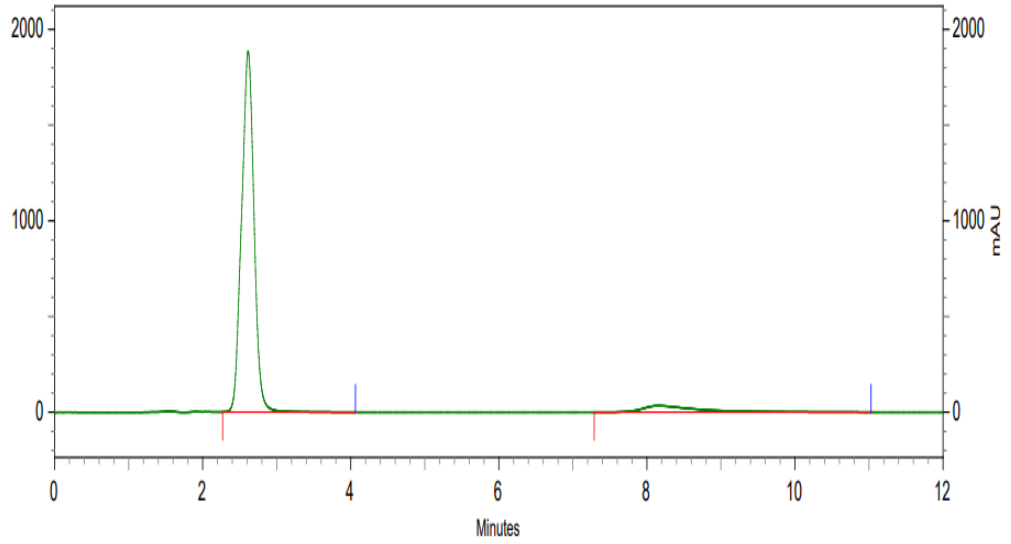

Fig. 9: HPLC Chromatogram of Formulation F3.

Table 13: Assay of Furosemide and Amlodipine of Formulation F3.

Name of drug	Retention Time	Area	Height	Theoretical Plates (USP)	Resolution (USP)	Asymmetry
Furosemide	8.153	1728088	33875	642	6.90328	2.18856
Amlodipine	2.613	22018424	1885029	1080	0.00000	1.01321
Total	10.766	23746512	1918904	1722	6.90328	3.20177

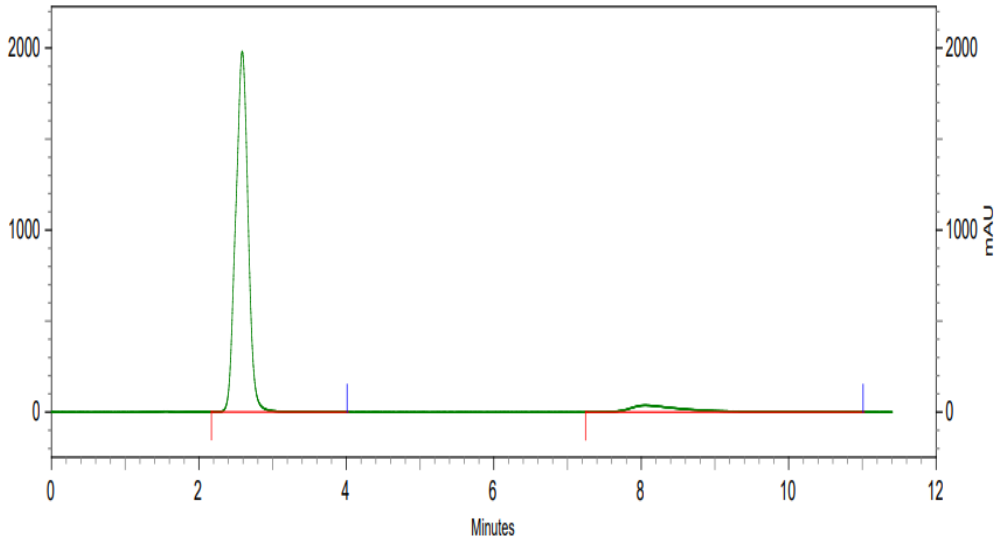

Fig. 10: HPLC Chromatogram of Formulation F4.

Table 14: Assay of Furosemide and Amlodipine of Formulation F4.

Name of drug	Retention Time	Area	Height	Theoretical Plates (USP)	Resolution (USP)	Asymmetry
Furosemide	8.053	1896686	37205	622	6.78229	2.26212
Amlodipine	2.588	23141630	1979757	1048	0.00000	1.00669
Total	10.641	25038316	2016962	1670	6.78229	3.26881

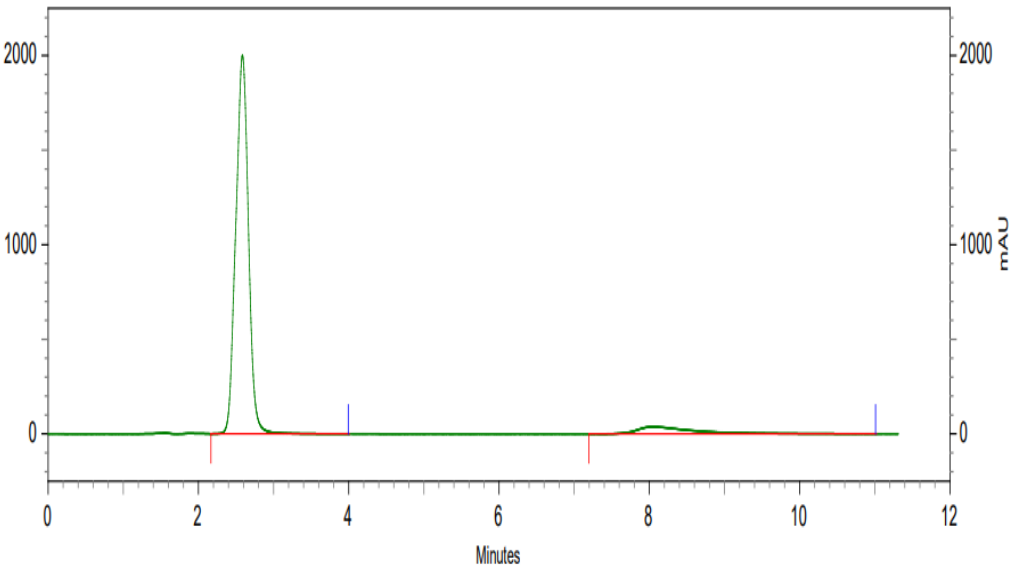

Fig. 11: HPLC Chromatogram of Formulation F5.

Table 15: Assay of Furosemide and Amlodipine of Formulation F5.

Name of drug	Retention Time	Area	Height	Theoretical Plates (USP)	Resolution (USP)	Asymmetry
Furosemide	8.045	1926187	37903	624	6.78648	2.28192
Amlodipine	2.585	23385263	1999382	1040	0.00000	1.01716
Total	10.63	25311450	2037285	1664	6.78648	3.29908

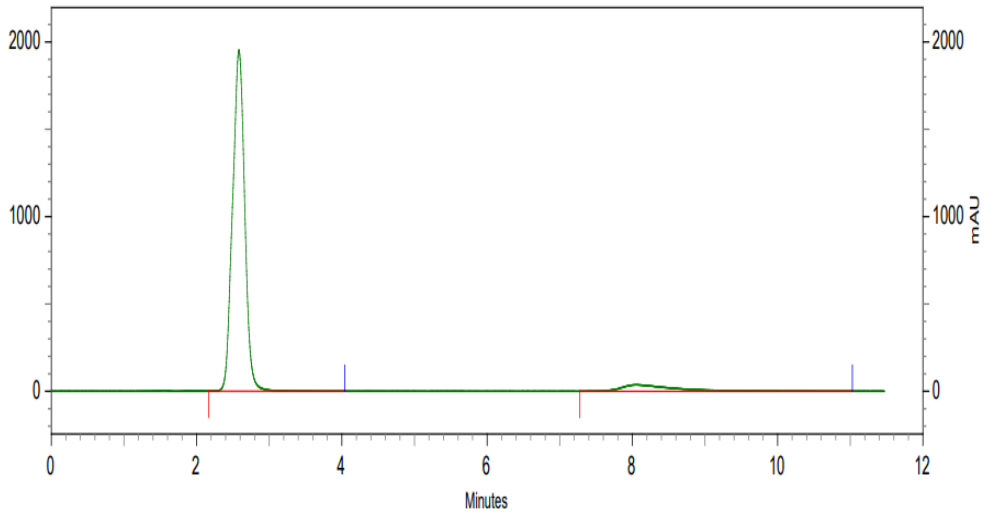

Fig. 12: HPLC Chromatogram of Formulation F6.

Table 15: Assay of Furosemide and Amlodipine of Formulation F6.

Name of drug	Retention Time	Area	Height	Theoretical Plates (USP)	Resolution (USP)	Asymmetry
Furosemide	8.053	1863222	36684	631	6.82996	2.26136
Amlodipine	2.583	22724328	1952295	1050	0.00000	1.01329
Total	11.113	24587550	1988979	1681	6.82996	3.27465

Table 16: Assay of Furosemide and Amlodipine ODTs.

No	Furosemide Recovery%*± SD	RSD%	Amlodipine Recovery%* ± SD	RSD%
F1	100.80 ± 0.983	0.976	97.56 ± 0.510	0.520
F2	99.84 ± 0.151	0.151	97.83 ± 0.740	0.756
F3	90.84 ± 0.503	0.554	91.64 ± 0.390	0.429
F4	99.57 ± 0.438	0.440	96.80 ± 0.001	0.001
F5	100.97 ± 0.313	0.310	97.81 ± 0.004	0.004
F6	97.52 ± 0.176	0.180	95.05 ± 0.001	0.001

Average of Three Determinations*.

The HPLC chromatogram of Furosemide and Amlodipine ODTs formulations were shown in Figures (7-12) and Tables (6-16). Assay of Furosemide and Amlodipine ODTs formulations following the procedure of the reported RP-HPLC method for the binary mixture of the standard substances and the formulated 6 formulations, the following data were obtained. Sample and standard concentrations of Furosemide and Amlodipine (20 and 5 µg/mL respectively), the results in the Table 16, showed that the assay of Furosemide ODTs (F1-F6) were found in the range between 90.84% to100.80 %. The assay of Amlodipine ODTs (F1-F6) were found in the range between 91.64% to 97.81%. The acceptable limit of Furosemide and Amlodipine content, and thus complied with the USP standard of drug content (90 to 110%). The results revealed that the assay of Amlodipine and Furosemide was within the acceptable limits.

***In-vitro* dissolution studies**

The in -vitro drug release of Amlodipine and Furosemide formulations ODTs were given in Tables 17and18.

Table 17: Percentage of Drug Release of Furosemide Formulations ODTs.

Formulation Code	Percentage Drug Release (%)		
	Time (min)		
	5	10	30
F1	42.90%	72.80%	69.94%
F2	43.26%	62.57%	75.08%
F3	55.15%	73.05%	88.83%
F4	76.51%	58.32%	73.01%
F5	75.27%	75.79%	75.27%
F6	60.58%	57.91%	57.12%

Table 18: Percentage of Drug Release of Amlodipine Formulations ODTs.

Formulation Code	Percentage Drug Release (%)		
	Time (min)		
	5	10	30
F1	82.82%	91.97%	92.35%
F2	90.72%	94.91%	97.56%
F3	86.57%	87.57%	88.46%
F4	82.74%	87.77%	94.70%
F5	83.29%	86.30%	83.29%
F6	71.28%	73.48%	84.27%

The in-vitro dissolution profile of Furosemide and Amlodipine is one of the most important experiments to prove if the ODTs are convenient to be used for rapid action. This study was applied to all formulations by using in phosphate buffer (pH 6.8) at time interval (5, 10, 30 minutes) digital dissolution tester at (37± 0.5°C).

Amlodipine and furosemide release were studied in Phosphate Buffer pH (6.8) for up to 30 minutes. The formulation F1 F2 F3 (crospovidone), F4 F5 F6 (sodium starch glycolate) were prepared along with microcrystalline cellulose, aspartame, magnesium stearate and sodium lauryl sulphate. The drug release of formulation F1, F2 and F3 was found to be 69.94 % ,75.08 % and 88.83% and the drug release of formulation F4 F5 F6 was found to be 73.01 % ,75.27 % and 57.12% at 30 minutes for Furosemide. The drug release of formulation F1, F2 and F3 was found to be 92.35%, 97.56% and 88.46% and the drug release of formulation F4 F5 F6 was found to be 94.70%, 83.29% and 84.27% at 30 minutes for Amlodipine.

From the above results and discussion, it was concluded that formulation of Orodispersible tablets of Furosemide and Amlodipine containing crospovidone such as F1, F2 and F3 can be taken as an optimized formulation of Furosemide Orodispersible tablets for drug release 42.90%, 43.26% and 55.15% release within 5 minutes while F1, F2 and F3 can be taken as an optimized formulation of Amlodipine Orodispersible tablets for drug release 82.82%, 90.72% and 86.57% release within 5 minutes. The formulations containing sodium starch glycolate such as F4, F5 and F6 can be taken as an optimized formulation of Furosemide Orodispersible tablets for drug release 76.51%, 75.27% and 60.58%release within 5 minutes while F4, F5 and F6 can be taken as an optimized formulation of Amlodipine Orodispersible tablets for drug release 82.74%, 83.29% and 71.28% release within 5 minutes. The present study shows that the dissolution rate of Furosemide and Amlodipine can be enhanced through the great extent by addition of superdisintegrant methods. The rapid drug dissolution might be due to easy breakdown of the particles due to porous structure formation after superdisintegration addition method and rapid absorption of drugs into the dissolution medium.

CONCLUSION

Furosemide and Amlodipine were selected as a model for preparation of Orodispersible Tablets ODTs by direct compression technique. Amlodipine is a long-acting calcium channel blocker (dihydropyridine) used as an anti-hypertensive and in the treatment of angina. Furosemide is a loop diuretic commonly used in adults, infants and children for the treatment of edematous states associated with congestive heart failure, cirrhosis of the liver and renal disease. Oral Furosemide may be used in adults for the treatment of hypertension alone or in combination with other antihypertensive agents.

Orodispersible tablets ODTs of Furosemide and Amlodipine were prepared by direct compression method using, and crospovidone and sodium starch glycolate as superdisintegrants. The tablets disintegrated rapidly in oral cavity and had acceptable hardness and friability. The *in-vitro* drug release from the tablets shows significantly improved drug dissolution. Hence it could be concluded that the superdisintegrant based Orodispersible tablets of Furosemide and Amlodipine would be quite effective in providing quick onset of action without need for water for swallowing or administration. In order to improve onset of action and increase bioavailability Furosemide and Amlodipine were developed as Orodispersible tablets. The results of *in-vitro* disintegration time of F4 and F2 was found to be 9 and 2 seconds and the drug release 90.72% and 76.51% at 5 minutes respectively indicated that the tablets dispersed rapidly in the mouth. It was concluded that F4 and F2 are the best formulations of Furosemide and Amlodipine Orodispersible Tablets ODTs drug delivery systems in order to increase onset of action and bioavailability of drug.

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