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HPLC ESTIMATION AND FORMULATION OF FAST DISSOLVING RAMIPRIL TABLET

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Abstract
The aim of the study was to formulate and develop method for the simultaneous estimation of fast dissolving ramipril tablet formulation using HPLC. The angle of repose of formulation F1 to F9 was determined to be 25.3, 25.1, 25.2, 25.4, 25.1, 25.0, 25.3, 25.4 and 25.6 respectively which indicates the flow of granules is good. The bulk density, Tapped density of powder (from formulation F1 to F9) was determined was found to be 0.45g/cc, 0.45g/cc, 0.43g/cc, 0.58g/cc, 0.45 g/cc,0.55 g/cc, 0.43 g/cc, 0.55 g/cc, 0.53 g/cc and 0.53g/cc, 0.53g/cc, 0.51g/cc, 0.68g/cc, 0.53 g/cc,0.62 g/cc, 0.51 g/cc, 0.65 g/cc, 0.60 g/cc respectively. The Carr's inddex was found to be 17.8, 17.8, 18.6, 17.2, 17.8, 12.7, 18.6, 18.2, 13.2 respectively, indicating F6 have lowest value i.e 12.7, thus it has better flow of powder than other formulation. The Hausner's ratio of formulation (F1-F9) was found to be 1.18, 1.18, 1.19, 1.17, 1.18, 1.13, 1.19, 1.18, and 1.13 respectively indicating formulation F6 and F9 have the lowest value (i.e. 1.13) and formulation F3 & F7 had highest value (i.e. 1.19), so formulation F6 and F9 has greater flow of powder among all these formulation., the thickness was around 3 and hardness was found to be 1.5 kg/cm. the friability of tablet was < 1%. The dissolution profile of formulation F1 to F9 was determined was found to be 96.35%, 95.21%, 97.26%, 94.25%, 93.91%, 95.0%, 93.09%, 90.58% and 101.55% respectively. From above data The formulation F3 (contain Polyethylene glycol 4000at greater amount), formulation F6 (containing PVK-30at greater amount), formulation F7, F8 and F9 (F9 (containing both Crosspovidone, MCC and Sodium glycolate)Crosspovidone) shows better release of drug among other formulation. The active content of each formulation was determined the found to be 98.07%, 94.70%, 96.39%, 96.40%, 96.45%, 98.57%, 97.88%, 98.08% and 102.5% from formulation F1 to F9 respectively.

Index Terms: Formulation, Evaluation, Hypertension, Ramipril, Drug, HPLC

1. Introduction:

Oral administration is a route of administration where a substance is taken through the mouth. It is the preferred route of administration of drug because of low cost of therapy ease of administration [1,2]. Because it is convenient and simple to consume, the oral route of medication administration is the most popular and recommended delivery technique. In the eyes of the patient, ingesting a dose form is a known and comfortable way to take medicine. Because of this, oral medicine is usually more successful than other methods of administration, including parenteral, in terms of patient compliance and, therefore, drug therapy [2]. When a medication

is taken orally, it dissolves in the stomach and/or intestinal fluids before passing through the GI tract's membranes and entering the bloodstream [3].
In order to improve the bioavailability of medications that are not very soluble in water, solid dispersions have been employed extensively to speed up the rate of dissolution. They are described as a solid-state dispersion of one or more active components in an inert matrix or carrier. A water-soluble polymer is typically combined with a drug substance to create a molecular, crystalline, or amorphous drug dispersion. The drug–polymer ratio determines the rate of dissolution, even though the metastable drug form dissolves more quickly than the crystalline state.

Alarmist esterase enzymes convert Ramipril into the a-live metabolite Ramiprilat.Angiotensin-II assembly is obscured by ACE inhibitors, which also shorten the breakdown of bradykinin by stopping the actions of an ACE angiotensin converting agitator. Because blood claret is driven into blood vessels, a reduction in the aftereffects of angiotensin-II results in a reduction of arterial bland ness arch to a reduction in absolute borderline resistance. Converting enzyme inhibitors decrease circulation angiotensin-II and enhance bradykinin, a powerful vasodilator.

The overall objective of this study will be to develop tablets of Ramipril using solid dispersion. PVK-30is a natural polymer with a high biological safety margin and increased production. Polyethylene glycol 4000 is biodegradable, biocompatible, and forms gel in water, therefore it appears to be gaining acceptance for the construction of matrix systems that release drugs sequentially via swelling to produce gel, diffusion of drug molecules, and eventually surface erosion of the matrix. [3].
1.1 Ramipril: An ACE inhibitor called Ramipril is used to treat hypertension and lower cardiovascular mortality in patients who are hemodynamically stable but have clinical symptoms of congestive heart failure after myocardial infarction [4].

The prodrug ramipril is a member of the class of drugs known as angiotensin-converting enzyme (ACE) inhibitors. The liver and, to a lesser extent, the kidneys convert it to ramiprilat. Angiotensin I (ATI) is converted to angiotensin II (ATII) by the enzyme ACE, which is strongly and competitively inhibited by ramiprilat. A vital part of the renin-angiotensin-aldosterone system (RAAS), ATII controls blood pressure. Ramipril can be used to treat nephropathy, hypertension, congestive heart failure, and to lower the risk of myocardial infarction, stroke, and death in people who are at high risk for cardiovascular events [5].

Table 3.1 Pharmacokinetic parameters of Ramipril [6, 7]

Category	***ACE inhibitor***
Molecular formula	$C_{23}H_{32}N_2O_5$
Molecular weight	416.5106 g/mol
Half life	2-4 hr
Bioavailability	73%

Solubility	Solubility in buffered aqueous solutions and polar solvents containing organic compounds.

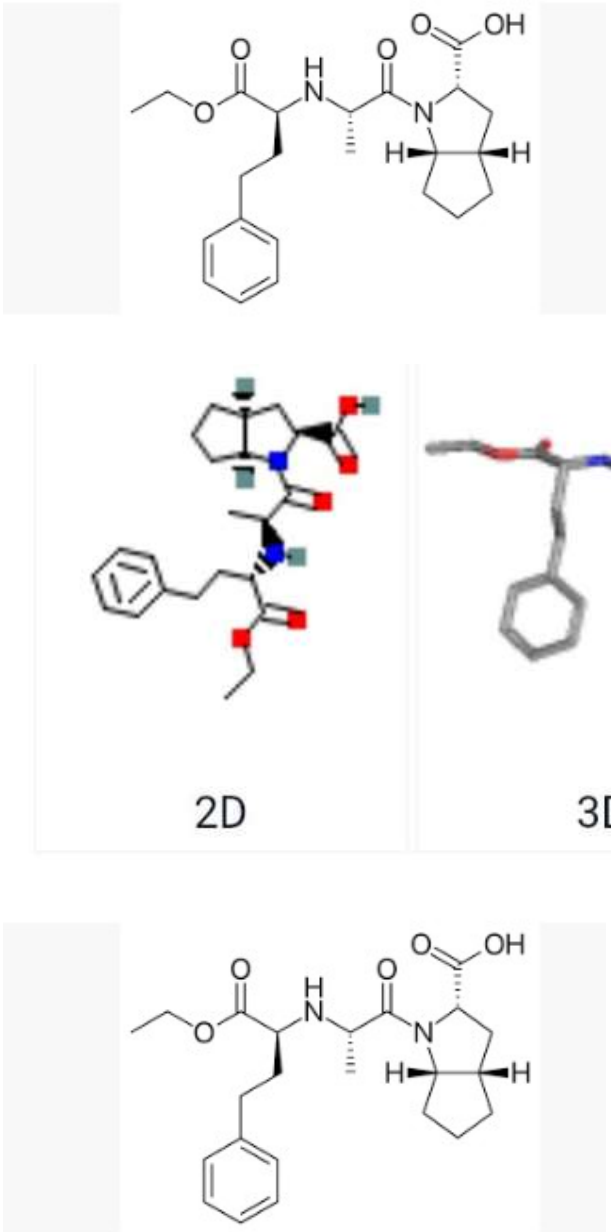

Fig No. 1 structure of Ramipril

1.2 Mechanism of Action:

By attaching to and blocking ACE, ramipril inhibits the RAAS system and stops angiotensin I from becoming angiotensin II. 5. The G-protein coupled receptors angiotensin receptor I

(AT1R) and angiotensin receptor II (AT2R) are less activated as angiotensin II plasma levels decline. [18]

Via a number of signaling pathways, AT1R promotes oxidative stress, fibrosis, inflammation, and vasoconstriction. 5. Gq coupling to the inositol triphosphate pathway, phospholipases C, A2, and D that aid in the synthesis of eicosanoid, Ca2+-dependent and MAP kinases Gi and G12/13, and finally the Jak/STAT pathway that promotes cell proliferation and the synthesis of extracellular matrix components are some of these. Reactive oxygen species are produced as a result of membrane-bound NADH/NADPH oxidase's enhanced activity brought on by AT1R activation. Ramipril's renoprotective, antihypertensive, and cardioprotective actions are mediated by decreased activation of this receptor, which lowers inflammation and vasoconstriction[4].

By activating phosphotyrosine phosphatases that inhibit MAP kinases, blocking Ca2+ channel opening, and inducing the synthesis of cGMP and nitric oxide, which results in vasodilation, AT2R counteracts the actions of AT1R. The Mas receptor, which is triggered by Ang (1–7), a subtype of angiotensin generated by plasma esterases from AngI or by ACE2 from AngII produced through a secondary pathway by tonin and cathepsin G, shares these opposing effects. While MasR mediates the majority of its impact, Ang(1–7) also activates AT2R.

Bradykinin breakdown is another effect of ACE. It is believed that the typical dry cough that occurs as a side effect of ACE inhibitor drugs is caused by the accumulation of bradykinin that results from ACE inhibition[4,5].

1.3 Absorbance:

There is at least 50–60% absorption.Label. Food slows down the GI tract's rate of absorption without changing the amount of absorption. When comparing oral and intravenous delivery, the absolute bioavailabilities of ramipril and ramiprilat were 28% and 44%, respectively. Opening the capsules and dissolving the contents in water, apple juice, or apple sauce did not affect the serum concentration of ramiprilat[6]

1.4 Pharmacodhynamics:

Like benazepril, fosinopril, and quinapril, ramipril is an ACE inhibitor. 5. The liver, the primary site of activation, and kidneys transform this inactive prodrug into ramiprilat. By counteracting the actions of the RAAS, ramiprilat lowers blood pressure. The RAAS is a homeostatic system that controls electrolyte and water balance as well as hemodynamics. The granular cells of the kidneys' juxtaglomerular apparatus release renin when sympathetic stimulation occurs or when renal blood pressure or blood flow is decreased [8.9].

Renin cleaves circulating angiotensinogen to ATI in the bloodstream, and ACE then cleaves ATII. ATII raises blood pressure through a variety of methods. First, it causes the adrenal cortex to release more aldosterone. By increasing the number of sodium channels and sodium-potassium ATPases on cell membranes, aldosterone promotes the reabsorption of water and sodium in the distal convoluted tubule (DCT) and collecting tubule of nephrons. Second, ATII

causes the posterior pituitary gland to release more vasopressin, also referred to as antidiuretic hormone or ADH. Through the insertion of aquaporin-2 channels on the apical surface of DCT cells and collecting tubules, ADH promotes more water reabsorption from the kidneys [6,9].

Third, ATII causes direct arterial vasoconstriction, which raises blood pressure. Vasoconstriction and myocyte contraction are the outcomes of a series of processes that are triggered by stimulation of the Type 1 ATII receptor on vascular smooth muscle cells. Along with these main effects, ATII stimulates hypothalamus neurons to cause the thirst response [15]. ACE inhibitors counteract RAAS-induced elevations in blood pressure by preventing the quick conversion of ATI to ATII. Bradykinin, a vasodilator, is similarly enzymatically deactivated by ACE (also called kininase II). By increasing vasodilation and lowering blood pressure, inhibiting the deactivation of bradykinin raises bradykinin levels and may prolong the benefits of ramiprilat[22].

1.5 Indication:

Ra in order to treat mild to severe hypertension. For hemodynamically stable people who get congestive heart failure within a few days of myocardial infarction, it may be used to lower cardiovascular mortality after myocardial infarction. To lower myocardial infarction, stroke, and death rates in people who are at high risk of cardiovascular events. For people with diabetes mellitus, hypertension, microalubinuria, or overt nephropathy to help reduce the progression of renal disease [21].

1.6 Metabolism:

Seventy-five percent of the entire metabolism of ramipril occurs in the liver. Via liver esterase enzymes, the active metabolite ramiprilat is produced by 25% of hepatic metabolism. Ramipril is converted to ramiprilat by 100% of renal metabolism. The glucuronides of ramipril and ramiprilat, as well as the metabolites diketopiperazine ester and diketopiperazine acid, are inactive [17.20].

1.7 Elimination:

About 60% of the dose is excreted in the urine as ramipril (<2%) and its metabolites after oral treatment. Feces contain around 40% of the dose, which includes both medicines and metabolites excreted by biliary excretion and unabsorbed medication. Patients with compromised renal function may have lower levels of ramipril excreted in their urine [25].

1.8 PVK-30

A synthetic water-soluble polymer derived from the monomer N-vinylpyrrolidone, povidone—also referred to as polyvinylpyrrolidone (PVP) or polyvidone—is used as a lubricant in eye drops and as a binder in numerous medicinal tablets. It serves a variety of purposes as an emulsifier, glue, and additive in numerous technological applications. When combined with iodine, povidone exhibits antiseptic qualities; povidone serves as a carrier, and iodine, a bactericidal component, primarily contributes to this action. [21, 25].

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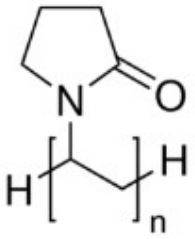

Fig. No. 3.2 Structure of PVK-30

Pharmacodynamics

Povidone is not a microbicidal agent in and of itself. Povidone-iodine has strong, quick, and all-around antibacterial qualities. Povidon-iodine's clinical efficacy on wound healing is still up for debate; in the few clinical studies that looked into the topic, topical application of the complex was linked to slower healing and mild to moderate discomfort upon application, but no serious infections[15,17].

Mechanism of action [9]

After free iodine is gradually released from the complex at the application site to react with the pathogen 1, the water-soluble compound known as povidone-iodine mediates a bactericidal or virucidal activity. To view the complete mechanism of action of the complex, please consult the Povidone-iodine medication article.

Applications [25]

- Polyethylene glycol 4000has remarkable rheological qualities, making it an ideal stabilizer for water-based systems. Its diverse applications vary from the food industry to oil drilling.
- Polyethylene glycol 4000is commonly used in salad dressings, sauces, gravies, dairy products, desserts, low-calorie snacks, and convenience meals.

2. Material and method:

2.1 Ingredients needed: National Healthcare Pvt. Ltd. Bara Nepal would provide a free sample of Ramipril and HPLC grade water. From India (Morefen Laboratory Limited) the Ramipril in standard raw material form were achieved.

2.2 Equipment needed: Shimadzu HPLC Prominence I LC-2030 with SPD 20 a detector, isocratic pump system, auto injection, and other features is used to design the method. A chromatography column made of stainless steel measuring 25 cm by 4.6 mm and filled with

octadecylsilyl silica gel (5 m) (Hypersil ODS). For the analytical process, additional instruments including an electronic balance (Schimadzu AP 135 W), a pH meter (Pico+ labindia), and a vacuum pump (PCI Analytical) are employed.

2.3 Preparation of Dapagliflozin Tablets:

For the fast-dissolving tablets of Ramipril, of nine formulation was prepared by weighting powder which are equivalent to 10 mg of Ramipril. Superdisintegrants, such as Crospovidone, were added to each formulation and stirred for ten minutes. The mixture mentioned above was run through sieve number 60. After adding lubricants like magnesium stearate and glidants like talc, the entire powder mixture was run through sieve number 60. Diluents, such as lactose, were then added. After that, the entire bulk powder was thoroughly combined in a mortar for fifteen minutes. A tablet punching machine was then used to compress the material into spherical tablets. Each batch of pills had a consistent weight. Using a tablet compression machine, each batch of 100 tablets was made by direct compression.

Contitunents of different formulations (F1-F9)

Formulation	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Ramipril	10	10	10	10	10	10	10	10	10
PVK-30 (Crosspovidone)	45	45	40	40	35	45	45	40	35
Polyethylene glycol 4000	45	45	50	50	55	0	0	0	0
Sodium starch glycolate	0	0	0	0	0	45	45	50	55
Talc	10	10	10	10	10	10	10	10	10
Magnesium stearate	10	10	10	10	10	10	10	10	10
Lactose	10	10	10	10	10	10	10	10	10
MCC	90	90	90	90	90	90	90	90	90
Total	220	220	220	220	220	220	220	220	220

2.4 Content of Active Ingredient/ Assay

2.4.1 Reference solution: Dissolve and dilute 100 mg of Ramipril WS to 100 ml with methanol. Dilute 1 ml of resulting liquid to 100 ml with methanol. With intermediate shaking sonicate it for 15 minutes.

2.4.2 Test solution: Crush 20 tablet. And Weigh accurately equivalent to 100 mg of powder tablet and transfer in 100 ml volumetric flask, dilute with diluents to volume. Dilute 1 ml of resulting liquid to 100 ml with methanol. With intermediate shaking sonicate it for 15 minutes

2.4.3 Chromatographic system: A stainless steel column C18 (4.6 mm × 15 mm) loaded with octadecylsilyl silica gel for chromatography (5 µ) (Hypersil ODS) is employed for separation. The sample injection volume was 10 µl, and the elution was seen at UV 224 nm.

2.4.4 Procedure: Inject the reference solution five times and the test solution. The test is not valid unless the column efficiency is not < 2000 theoretical plates, tailing factor is not > 2.0, and the RSD for replicate injection is not > 2.0%. Measure the peak response and calculate the content of Ramipril using following formula.

$$Assay\ \% = \frac{Area\ of\ test}{Avg.\ area\ of\ std.} \times \frac{Wt.\ of\ std.}{100} \times \frac{1}{100} \times \frac{100}{1} \times \frac{100}{Wt.\ of\ test} \times Avg.\ wt. \times \frac{Potency\ of\ std}{Claim}$$

3. Result and discussion:

3.1 Identification:

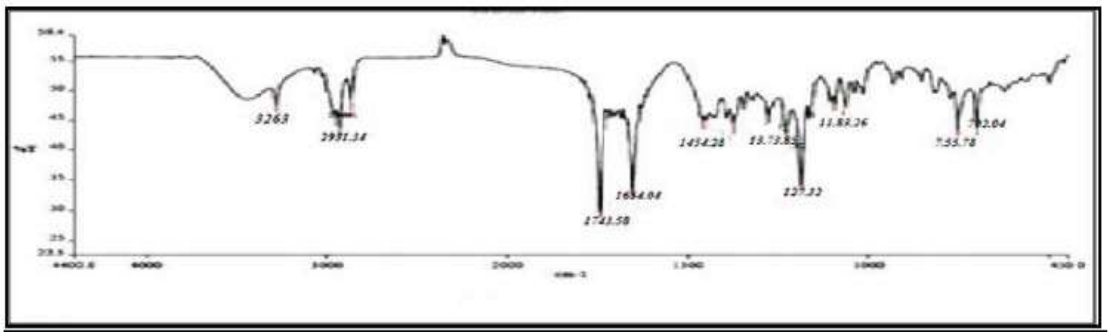

Fig. No. 3.1: IR Spectrum of Ramipril (Standard)

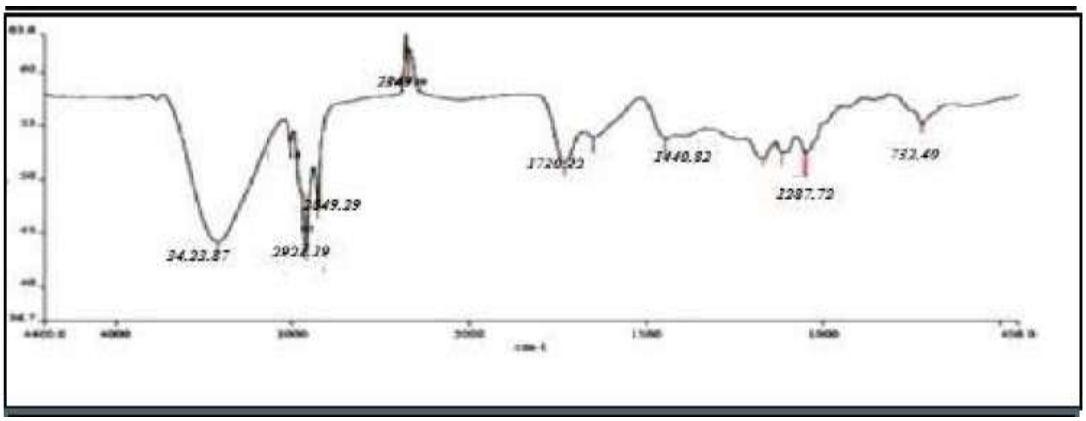

Fig. No. 3.2: IR Spectrum of Ramipril (Test)

Figures No. 3.1 and 3.2 respectively, display the IR spectrum of Ramipril (Standard) and Ramipril (Test). The spectrum shows that there is no interference/disecption working standard (Ramipril). The approach was genuiene to Ramipril because the IR spectrum of test is corresponded with that obtained with Ramipril Propandiol (Working standard).

Table 3.1: Characterized of granules and tablets of Dapagliflozin

Specification	F1	F2	F3	F4	F5	F6	F7	F8	F9
Angle of repose	25.3	25.1	25.2	25.4	25.1	25.0	25.3	25.4	25.6
Bulk density(g/cc)	0.45	0.45	0.43	0.58	0.45	0.55	0.43	0.55	0.53
Tap density (g/cc)	0.53	0.53	0.51	0.68	0.53	0.62	0.51	0.65	0.60
Carr's index	17.8	17.8	18.6	17.2	17.8	12.7	18.6	18.2	13.2
Hausner's ratio	1.18	1.18	1.19	1.17	1.18	1.13	1.19	1.18	1.13
Weight variation (mg)	221.9	221.8	220.4	223.6	222.4	223.4	221.3	222.6	222.8
Friability (%)	0.38	0.70	0.01	0.03	0.10	0.07	0.34	0.11	0.14
Thickness (mm)	3	3	3	3	3	3	3	3	3
Hardness (kg/cm)	1.5	1.5	1.5	1.5	1.5	1.4	1.5	1.5	1.5
Assay (%)	98.88	98.70	99.19	97.91	98.82	98.73	99.33	98.76	99.86

3.2 Weight variation:

The weight variations of different formulations (F1 to F9) was evaluation by weighing 10 tablets of each formulation and found to be 221.9 mg, 221.8 mg, 220.4 mg, 223.6mg, 222.4 mg, 223.4 mg, 221.3 mg, 222.6 mg and 222.8 mg respectively, which was within the limit variation (i.e. ± 10%) as per IP 2022. The details are shown in Table 3.2

Table 3.2: Weight variation of different formulation

SN.	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
1	220	222	223	225	224	223	222	220	226
2	220	222	223	224	220	223	220	220	226
3	222	210	220	224	226	226	222	224	222
4	225	221	220	225	225	223	223	225	225
5	220	222	223	220	225	228	222	227	224
6	223	224	210	225	224	223	220	220	220
7	224	222	218	220	220	225	222	226	225
8	225	228	224	225	220	223	220	223	220
9	220	222	223	225	220	220	222	221	220
10	220	225	220	223	220	220	220	220	220
Avg	221.9	221.8	220.4	223.6	222.4	223.4	221.3	222.6	222.8
Std.	2.183	4.638	4.141	2.011	2.590	2.458	1.15	2.756	2.658
% variation	0.109	0.109	0.102	0.118	0.112	0.117	0.106	0.113	0.114

3.3 Thickness:

The Thickness of different formulations (F1 to F9) was evaluated by vernier caliper using 6 tablets of each formulation and found to be 3 mm, 3 mm, 3 mm, 3 mm, 3 mm, 3 mm, 3 mm, 3 mm, and 3 mm respectively, which was shown in Table 3.3

Table 3.3 Thickness of different formulations

S.N.	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	3.1	3	3	3	3	3	2.6	2.6	3
2	3.2	2.8	3	3.2	3.3	3	2.8	2.7	3
3	2.9	2.8	2.6	3.2	3	3	3	2.9	3.1
4	2.8	3	3	3	3	3.2	2.9	2.5	3
5	3	3.1	3.1	3	3.1	3.2	3	3.2	3.3
6	3.2	3.2	3	3	3	3	3	3	3.4
Avg.	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**
SD	**0.163**	**0.160**	**0.176**	**0.103**	**0.121**	**0.103**	**0.160**	**0.264**	**0.175**

3.4 Hardness:

The hardness of different formulations (F1 to F9) was evaluated by breaking force tester using 6 tablets of each formulation and found to be 1.5 kg/cm, 1.5 kg/cm,, 1.5 kg/cm, 1.5 kg/cm, 1.5 kg/cm,, 1.4 kg/cm, 1.5 kg/cm, 1.5 kg/cm, and 1.5 kg/cm respectively, which was shown in Table 3.4

Table 3.4 Hardness of different formulations

S.N.	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	1.5	1.6	1.4	1.6	1.4	1.4	1.5	1.4	1.5
2	1.6	1.4	1.4	1.4	1.5	1.4	1.5	1.5	1.5
3	1.4	1.5	1.5	1.6	1.5	1.4	1.5	1.5	1.5
4	1.6	1.5	1.5		1.5	1.5	1.4	1.5	1.6
5	1.4	1.5	1.5	1.6	1.4	1.5	1.4	1.4	1.5
6	1.6	1.4	1.4	1.4	1.4	1.4	1.4	1.6	1.6
Avg.	**1.5**	**1.5**	**1.5**	**1.5**	**1.5**	**1.4**	**1.5**	**1.5**	**1.5**
Sd	**0.098**	**0.075**	**0.055**	**0.110**	**0.055**	**0.052**	**0.055**	**0.075**	**0.052**

3.5 Friability test:

The hardness of different formulations (F1 to F9) was evaluated by Friability test apparatus using 10 tablets of each formulation and found to be 0.38%, 0.70%, 0.01%, 0.03%, 0.10%, 0.07%, 0.34%, 0.11% AND 0.14% respectively, which was found within limit of Not more than 1%.

3.6 Dissolution test:

All of the manufactured tablets underwent in vitro dissolving tests using the USP paddle method at 50 rpm in 900 ml of phosphate buffer (pH 6.8) as the dissolution medium, which was kept at 37±0.5 °C. At the designated intervals, a 5 ml aliquot was taken out, filtered with whatman filter paper, and then spectrophotometrically measured at 210 nm. To keep the volume constant throughout the test, an equivalent volume of freshly heated medium (37 °C) was added to the dissolution media following each measurement.

Reference solution preparation: It will be prepared by dissolving and diluting 100 mg of Ramipril WS to 100 ml with methanol. Further it will be with 1 ml of this solution with 100 ml with dissolution medium.

$$Amount\ in\ \% = \frac{Abs.\ of\ test}{Abs.\ of\ std.} \times \frac{Wt.\ of\ std.}{100} \times \frac{1}{100} \times \frac{900}{10} \times Potency\ of\ std.$$

The in vitro dissolution test was carried out for all the formulated batches in 900 ml phosphate buffer (pH 6.8) at 37 ± 0.5º C at 50 rpm. Approximately 5 ml sample was withdrawn from each basket after 30 minutes and was found to be 96.35% for formulation 1 (F1) the % drug release of formulation F2 was found to be 95.21%. The % drug release of formulation F3 was found to be 97.26%. Such that the % drug release of formulation F4 was found to be 94.25%. The % drug release of formulation F5 was found to be 93.91%. The % drug release of formulation F6 was found to be 95.0% .the % drug release of formulation F7 was found to be 93.09%. The % drug release of formulation F8 was found to be 90.58%. The % drug release of formulation F9 was found to be 101.55%. From above data the formulation F3 (contain Polyethylene glycol 4000at greater amount), formulation F6 (containing PVK-30at greater amount), formulation F7, F8 and F9 (containing both Polyethylene glycol 4000and sodium glycolate) shows better release of drug among other formulation.

Statistical Analysis of Data Obtained From Dissolution of Different Formulated Batches of Dapagliflozin

The release kinetic analysis of different formulated batches of Dapagliflozin (F1- F9) were calculated by comparing profile of various formulation (F1- F9). the value of R^2 of different formulation (F1 – F9) were stated in table 3.5 the value of R2 of formulation F1 to F9 was greater(0.968, 0.954, 0.983, 0.943, 0.938, 0.984, 0.972, 0.978, 0.982) in first order kinetics among all statistical analysis; that means, the formulations followed first order kinetics. The release of drug was depend on the concentration of polymer, as the concentration of polymer increases the release rate decreases.

Similarly, the drug release data were treated according to Zero order, first order, Higuchi kinetics and Pappas model which are summarized in table 3.5

The zero order rates describe the systems where the drug release rate in independent of its concentration. The first order represents the release from systems in which the release rate varies with concentration. Higuchi's model presents drug release from an insoluble matrix as a square root of a time-dependent mechanism based on Fick's diffusion. The release constant was

calculated from the slope of the appropriate plots, and the regression coefficient (R^2) was determined which is shown in table 3.5. It was found that the in vitro drug release of Dapagliflozin was best explained by first order and Higuchi's model , as the plots showed the highest linearity (R^2=0.984) and Higuchi model (R^2=0.997),followed by zero order (R^2=0.770) and Pappas model (R^2=0.997).this explains why the drug diffuses at a comparatively slower rate as the distance for diffusion increases, which referred to as square root kinetics (Higuchi's model) and also indicates that the concentration plays a m ajor role in the drug release, which referred to first order kinetics.

Table 3.5 Release Kinetics of Dapagliflozin Tablet

R^2				
Formulation	**Zero order**	**First order**	**Higuchi**	**Peppas**
F1	0.531	0.968	0.581	0.911
F2	0.591	0.954	0.631	0.888
F3	0.668	0.983	0.968	0.994
F4	0.769	0.943	0.581	0.888
F5	0.578	0.938	0.621	0.869
F6	0.419	0.984	0.989	0.991
F7	0.607	0.972	0.997	0.998
F8	0.698	0.978	0.995	0.997
F9	0.770	0.982	0.988	0.996

3.7 Assay:

Reference solution: 100 mg of Ramipril WS was dissolved to 100 ml with methanol. Further 1 ml of resulting liquid was dilute to 100 ml with methanol. With intermediate shaking sonicate it for 15 minutes.

Test solution: After Crushing 20 tablet. 100 mg of powder tablet approximetly was weighed and transfer in 100 ml volumetric flask, diluted with diluents to volume. 1 ml of resulting liquid was diluted to 100 ml with methanol. With intermediate shaking sonicate it for 15 minutes

Chromatographic system: A stainless steel column C18 (4.6 mm × 15 mm) loaded with octadecylsilyl silica gel for chromatography (5 µ) (Hypersil ODS) is employed for separation. The sample injection volume was 10 µl, and the elution was seen at UV 224 nm.

Procedure: Inject the reference solution five times and the test solution. The test is not valid unless the column efficiency is not < 2000 theoretical plates, tailing factor is not > 2.0, and the RSD for replicate injection is not > 2.0%. Measure the peak response and calculate the content of Ramipril using following formula.

$$Assay\ \% = \frac{Area\ of\ test}{Avg.\ area\ of\ std.} \times \frac{Wt.\ of\ std.}{100} \times \frac{1}{100} \times \frac{100}{1} \times \frac{100}{Wt.\ of\ test} \times Avg.\ wt. \times \frac{Potency\ of\ std}{Claim}$$

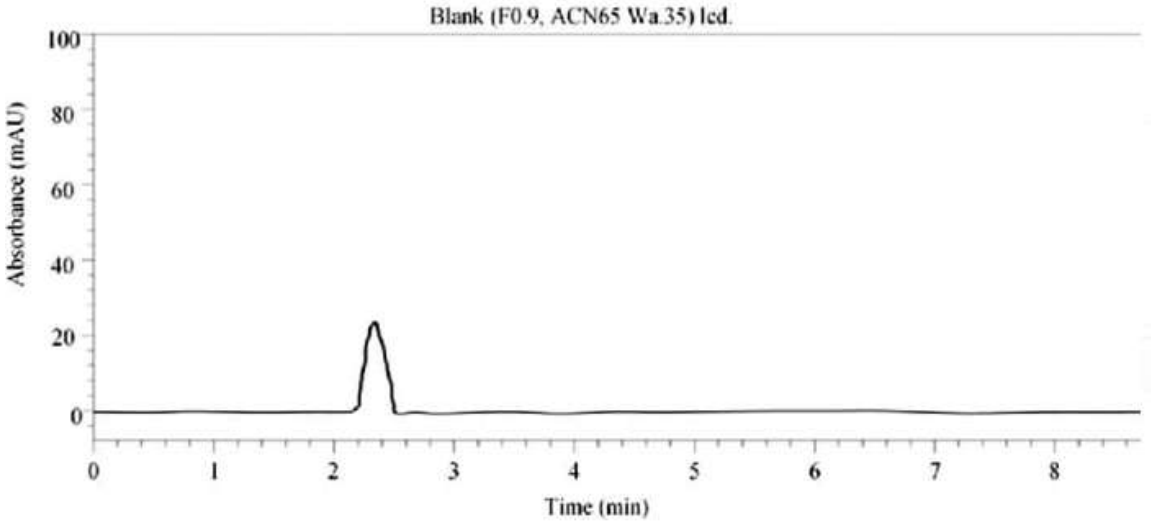

Fig No. 3.3 Blank

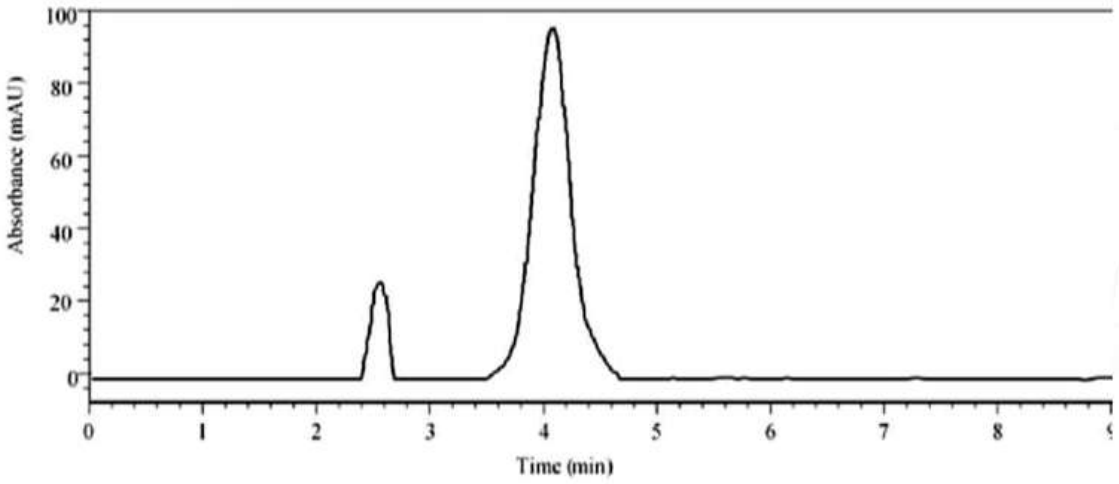

Fig No. 3.4 Chromatogram of Standard (Ramipril)

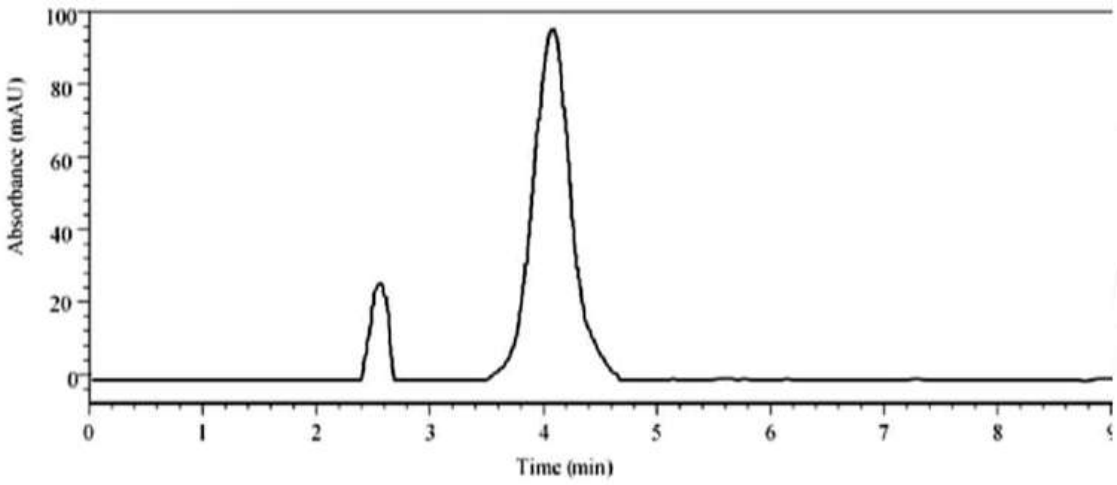

Fig No. 3.4 Chromatogram of Test (Ramipril)

For Formulation F1:

$$Assay\ \% = \frac{1443681}{1446839} \times \frac{100.3}{100} \times \frac{1}{100} \times \frac{100}{1} \times \frac{100}{2219} \times 221.9 \times \frac{98}{10} = 98.07\%$$

For Formulation F2:

$$Assay\ \% = \frac{1394055}{1446839} \times \frac{100.3}{100} \times \frac{1}{100} \times \frac{100}{1} \times \frac{100}{2218} \times 221.8 \times \frac{98}{10} = 94.70\%$$

For Formulation F3:

$$Assay\ \% = \frac{1418868}{1446839} \times \frac{100.3}{100} \times \frac{1}{100} \times \frac{100}{1} \times \frac{100}{2204} \times 220.4 \times \frac{98}{10} = 96.39\%$$

For Formulation F4:

$$Assay\ \% = \frac{1418993}{1446839} \times \frac{100.3}{100} \times \frac{1}{100} \times \frac{100}{1} \times \frac{100}{2236} \times 223.6 \times \frac{98}{10} = 96.40\%$$

For Formulation F5:

$$Assay\ \% = \frac{1419834}{1446839} \times \frac{100.3}{100} \times \frac{1}{100} \times \frac{100}{1} \times \frac{100}{2224} \times 222.4 \times \frac{98}{10} = 96.45\%$$

For Formulation F6:

$$Assay\ \% = \frac{1450879}{1446839} \times \frac{100.3}{100} \times \frac{1}{100} \times \frac{100}{1} \times \frac{100}{2234} \times 223.4 \times \frac{98}{10} = 98.57\%$$

For Formulation F7:

$$Assay\ \% = \frac{1440779}{1446839} \times \frac{100.3}{100} \times \frac{1}{100} \times \frac{100}{1} \times \frac{100}{2213} \times 221.3 \times \frac{98}{10} = 97.88\%$$

For Formulation F8:

$$Assay\ \% = \frac{1443799}{1446839} \times \frac{100.3}{100} \times \frac{1}{100} \times \frac{100}{1} \times \frac{100}{2226} \times 222.6 \times \frac{98}{10} = 98.08\%$$

For Formulation F9:

$$Assay\ \% = \frac{1509889}{1446839} \times \frac{100.3}{100} \times \frac{1}{100} \times \frac{100}{1} \times \frac{100}{2218} \times 221.8 \times \frac{98}{10} = 102.5\%$$

The reference solution five times and test solution of each formulation was injected the found to be theoretical plate was more than 2000 and tailing factor was less than 2. The retention time for replicate njection was found to be about 5 minutes. The peak was observed around 5 minutes. The active content of each formulation was determined the found to be 98.07%, 94.70%, 96.39%, 96.40%, 96.45%, 98.57%, 97.88%, 98.08% and 102.5% from formulation F1 to F9 respectively.

4. Conclussion

The aim of the study was to formulate and develop method for the simultaneous estimation of fast dissolving ramipril tablet formulation using HPLC. The angle of repose of formulation F1 to F9 was determined to be 25.3, 25.1, 25.2, 25.4, 25.1, 25.0, 25.3, 25.4 and 25.6 respectively which indicates the flow of granules is good. The bulk density of powder (from formulation F1 to F9) was determined was found to be 0.45g/cc, 0.45g/cc, 0.43g/cc, 0.58g/cc, 0.45 g/cc,0.55 g/cc, 0.43 g/cc, 0.55 g/cc, 0.53 g/cc respectively. The Tapped density of powder (from formulation F1 to F9) was determined was determined to be 0.53g/cc, 0.53g/cc, 0.51g/cc, 0.68g/cc, 0.53 g/cc,0.62 g/cc, 0.51 g/cc, 0.65 g/cc, 0.60 g/cc respectively. The Carr's inddex of formulation (F1 to F9) was determined and found to be 17.8, 17.8, 18.6, 17.2, 17.8, 12.7, 18.6, 18.2, and 13.2 respectively. In which formulation F6 have lowest value i.e 12.7, thus it has better flow of powder than other formulation. The Hausner's ratio of formulation (F1-F9) was determined and was found to be 1.18, 1.18, 1.19, 1.17, 1.18, 1.13, 1.19, 1.18, and 1.13 respectively. In which formulation F6 and F9 have the lowest value (i.e. 1.13) and formulation F3 anf F7 had highest value (i.e. 1.19), so formulation F6 and F9 has greater flow of powder among all these formulation. The average weight of tablets was determined to be around 160-161 mg. the thickness was around 3 and hardness was found to be 1.5 kg/cm. the friability of tablet was < 1%. The dissolution profile of formulation F1 to F9 was determined was found to be 96.35%, 95.21%, 97.26%, 94.25%, 93.91%, 95.0%, 93.09%, 90.58% and 101.55% respectively. From above data the formulation F3 (contain Polyethylene glycol 4000at greater amount), formulation F6 (containing PVK-30at greater amount), formulation F7, F8 and F9 (containing both Polyethylene glycol 4000and sodium alginate) shows better release of drug among other formulation. The active content of each formulation was determined the found to be 98.07%, 94.70%, 96.39%, 96.40%, 96.45%, 98.57%, 97.88%, 98.08% and 102.5% from formulation F1 to F9 respectively.

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