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Design of Novel Bilayer Oral Films for Treatment of Acute Hypertension

Manjunath B Mendon[1*] , Roopa Karki[1]

1.NIMS University, Jaipur, (RJ) - India

ABSTRACT

The main aim of research work was to design novel bilayer fast dissolving films as a drug delivery system for treatment of severe hypertension and acute cases like angina pectoris. In present work two incompatible drugs Amlodipine and Benazapril was combined in single dosage form using impermeable membrane. The thin films of both drugs were prepared by using different concentration of polymers, plasticizers and super disintegrants. The films were casted in to bilayer films using impermeable membrane. These prepared Bilayer films were characterized on basis of thickness, folding endurance, tensile strength and dissolution time. On basis of study it was found that the optimized film dissolves within 60 sec. and both drugs do not show interaction during preparation and stability period. The proposed novel films will deliver the two incompatible drugs and releases the drug quickly thus can be preferred in hypertension emergencies.

Keywords: Bilayer oral films, Hypertension, Amlodipine, Benazapril

*Corresponding Author Email: manjunath.mendon@gmail.com

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INTRODUCTION

Oral dissolving films (ODF)

Some patients have difficulties in swallowing or chewing solid dosage which forms risk or fear of chocking so this is a major problem in the use of tablets. Oral dissolving film is a new drug delivery system for oral delivery of drug. Oral film a type of film which is used in acute condition such as pain, antiemetic, anti-migraine, anti-hypertension, congestive heart failure, and Asthma etc. oral dissolving film has gained popularity due to its availability in various size and shape[1]. Oral dissolving films are intended to disintegrate or dissolve within seconds. They offer advantages such as administration without water, rapid onset of action and convenience of dosing. For fast dissolving active pharmaceutical ingredients absorption is possible through the oral mucosa and may improve bioavailability[2].

The concept of oral dissolves film

1. This delivery system consists of a thin film.
2. After placing it on the top of the tongue, the film dissolves within seconds, promoting first pass metabolism as compared to tablet and other immediate release oral solid dosage forms, and may increase the bioavailability of drug[3].
3. FDF dissolves in the mouth like a cotton candy.

Bilayer formulations either as tablet or films (Buccal or fast dissolving oral films) is a need of time for successful development of Modified Or Instant release formulation along with various features to provide successful drug delivery system. Bilayer formulations either as tablet or films (Buccal or fast dissolving oral films can be a primary option to avoid chemical incompatibilities between API by physical separation, and to enable the development of different drug release profiles.

Advantages of the tablet or films (Buccal or fast dissolving oral films) are

It is the dosage form and offers the greatest capabilities of all oral dosage form for the greatest dose precision and the least content variability, Cost is lower compared to all other oral dosage form, Lighter and compact, Easiest and cheapest to pack and strip, Easy to dissolve on tongue with least tendency for hang up, Objectionable odour and bitter taste can be masked by various techniques, Suitable for large scale production, Greatest chemical and microbial stability over all oral dosage form. Product identification is easy and rapid requiring no additional steps when employing an embossed and/or monogrammed punch face.

Concept of Bilayer films

Bilayer formulations either as tablet or films (Buccal or fast dissolving oral films) is a need of time for successful development of Modified Or Instant release formulation along with various features to provide successful drug delivery system. Bilayer formulations either as tablet or films (Buccal or fast dissolving oral films) can be a primary option to avoid chemical incompatibilities between API by physical separation, and to enable the development of different drug release profiles.[4-6]

Objectives of Bilayer formulations as tablet or films (Fast dissolving oral films):

- To separate incompatible active pharmaceutical ingredient (APIs) from each other, to control the release of API from one layer by utilizing the functional property of the other layer (such as, osmotic property).
- To control the delivery rate of either single [1]or two different active pharmaceutical ingredient(s).
- To modify the total surface area available for API layer either by sandwiching with one or two inactive layers in order to achieve Fast Disintegration/swellable/erodible barriers for modified release.
- To administer fixed dose combinations of different APIs prolong the drug product life cycle, fabricate novel drug delivery systems such as chewing device, buccal/ mucoadhesive delivery systems, and floating tablets for gastro-retentive drug delivery.

MATERIAL AND METHODS

Material

The Amlodipine and benazapril drug was obtained as gift samples from Amneal formulations, ahemdabad. The HPMC K-15, Pullulan, cross povidone and cross carmellose sodium was obtained as a gift samples from trupati balaji formulations. Rest all material were purchased from Hi media and CDH laboratory. The all material was of analytical grade.

Methods

The methodology adopted for preparation BFDOF were completed as following steps:

- Preparation of oral film of drug A as film A
- Preparation of oral film of drug B as film B
- Moistening by suitable solvent of adjoining surfaces of film A and film B
- Rolling of both layer
- Drying and cutting of BFDOF

Preparation of Films by Solvent Casting Method

The all Solid Material properly weigh by pre calibrated electronic balance (Citizen) and all liquid materials were also measured properly. The all pre weighed material were mix properly on mechanical stirrer at controlled speed. The all material was added in solvent and then liquid material was added during stirring. The stirring speed of stirrer was kept at 200-500 RPM and temperature was set at 25-30^{0}c. The mixing was continue till clear, transparent solution was obtained. After complete mixing of all ingredients the clear solution was sonicated to remove dissolved air which may appear during mixing process. Three cycle of sonication of 5-10 sec was performed for complete removal of air. A 20.0 x8.0 cm sized Film casting glass reservoir was fabricated having depth of 0.5cm. This sized Film casting glass reservoir will produce forty 2.0x2.0 cm size films. Then the solution was carefully poured in to glass reservoir uniformly to ensure uniform thickness of film. Preliminary study suggests that 40 ± 1.0 ^{0}C for 12 hrs adequately dry the film. The drying of film was done under controlled evaporation to assure no air entrapped during the drying process. After complete drying of film, the film was carefully removed from glass reservoir. The removal was easily performed as already oil was used for lubrication. After complete removal of film it was ready to cut in appropriate size. After complete removal of films it was cut in to appropriate size for administration in oral cavity. The films were cut in to 2 X 2 cm ^{2}. [7]

Figure:1 Film ready to cut in appropriate size

After complete removal of films it was cut in to appropriate size for administration in oral cavity. The films were cut in to 2 X 2 cm ^{2}.

Optimization of Films:

The optimization is basic step for research. The optimization was performed by EVOP (Evolutionary Operation) method. This method is widely used in research and industry. The manufacturing of films depends on many factors such as type and concentration of film formers, type and concentration of plasticizers, type and concentration of super disintegrating agents, type of methods employed in manufacturing and type of solvent system etc.[8]

Out of all factors, following three important factors were selected for optimization process.

1. Selection of Film Forming Agents
2. Selection of Plasticizers
3. Selection of Super disintegrating agents

The optimization of films was firstly done without drugs. The optimizations of all factors were done on the basis of General Appearance, Thickness, Folding endurance, Tensile strength, and % elongation and disintegration time.

Characterization of Bi Layer Fast Dissolving Films

Determination of thickness

Thickness of film was most important parameter because uniformity of thickness determined content uniformity of BFDOF. The thickness of film was determined by DIGITAL THICKNESS GAUGE (Moore & Wright, Germany) after proper drying of bi layer films. The thicknesses of one batch were determined from nine different places to assure the uniformity.[9]

Size of Film

Size of tongue is about 2.5 x2.0 cm, to provide sufficient space for dissolving in oral cavity by putting film on tongue for swishing or hydrating with saliva , size 2.0 x 1.5 cm were concluded as unit dose of BFDOF.

Disintegration Time

As per the guidance provided by Center for Drug Evaluation and Research (CDER) USFDA for Orally disintegration films should be less than 30 seconds (half minute), that guidance were objective for this present study. This was a quality guideline for qualitative guideline for quality control test at development stage. A pharmacopoeial disintegrating test apparatus (Labindia) were used to determining the disintegration time *in-vitro.*[8]

Tensile Strength and %-Age Elongation Determination

The load [N] and elongation [%] were measured during tensile test by a Tensile Strength and %-Age Elongation testing apparatus (Winsar chennai).Each strip of film was cut and prepared so that 2.0x2.0 cm2 remain for testing ,other portion were clamped between the tensioning tools.[7,10]

Folding Endurance

Folding endurance were determined by repeating folding of the oral dissolving films initially as in single layer and then finally for bilayer fast dissolving oral films. Folding endurance of the films is determined by automatic folding endurance apparatus. The final shaped oral films were analyzed in this apparatus individually for each batch.[11]

Drug Content and Content Uniformity

As per pharmacopeial assay method the drug content and content uniformity were determined for each API during single layer optimization and during final batches of different combinations. Content uniformity was determined by selecting three samples of film.[12]

Dissolution Studies

A modified shaking water bath dissolution method was employed to determining the drug release profile of the film. The shaking water bath apparatus (100 strokes per minute) consist of a water bath, thermostatically controlled at 37±0.5 oC and a mechanical shaker platform onto which bottle holder plate were positioned. Glass bottles (125ml), the secured holders of holder plate. 100 ml of PBS (Phosphate Buffered Solution) having the pH 6.5 equilibrated to 37±0.5 ^{0}C were used for dissolution medium. A specified time intervals, 2.0 ml aliquots of samples were taken out from each vessel (Three) using a syringe and filtered through 0.45 µ Millipore filter. An equal amount of fresh pH6.5 PBS were used to replaced into each vessels to ensure a constant volume of dissolution medium throughout the dissolution study.[8]All dissolution samples were analyzed as predetermined specific wavelengths for individual API.

Stability Studies

Stability studies of BFDOF as new drug product were determined by ICH stability guidelines provided in Q1A. The choice of test conditions defined in guideline is based on an analysis of the effects of climatic conditions in the three regions of the EC, Japan and the United States. The mean kinetic temperature in any part of the world can be derived from climatic data, and the world can be divided into four climatic zones, I-IV. This guideline addresses climatic zones I and II. The principle has been established that stability information generated in any one of the three regions of the EC, Japan and the United States would be mutually acceptable to the other two regions, provided the information is consistent with this guideline and the labeling is in accord with national/regional requirements.

***In-vivo* Studies**

All the experimental procedures were carried out in accordance with committee for the purpose of control and supervision of experiments on animal (CPCSEA) guidelines. All the experimental procedures were approved by the institutional animal ethical committee (IAEC). (IAEC/SCOPE/11-12/81)

Sixty Male albino rabbits weighing 2 to 3 kg were used in all studies. The animals were kept under standard laboratory conditions in 12 h light/dark cycle at 25 ± 2 °C. Animals were provided with pellet diet (Lipton, India) and water *ad libitum.* Animals were marked with picric acid solution for easy identification.[13]

Conditioning/Training of Animals

For conducting the BP measurement studies, the animals were required to be kept in a restrainer. It had only one side open for entry/exit of the animal with proper ventilation at all other sides. As the animals were unaccustomed to remain in the restrainer in a calm and non-aggressive manner, animals were trained for their stay in the restrainer as a slight movement in and aggression by the animal would have led to variation in the BP readings. For this, animals were inserted in the restrainer headlong until the whole body got conveniently accommodated inside. The restrainer was locked by screwing the open side of the apparatus leaving the tail outside. The exercise was repeated several times until the animals learnt to stay in restrainer non aggressively and familiarized with the conditions.

Measurement of Initial Systolic BP of Rabbits

The initial BP of all the animals was recorded using Non-invasive blood pressure apparatus (Biopac Systems, Inc Santa Barbara, USA). The restrainer carrying the animals was placed in the restrainer with tail protruding out. Systolic blood pressure was measured indirectly in conscious and slightly restrained Rabbit by the tail cuff method. An average of ten consecutive readings was noted.[14]

Measurement of Initial other parameters of Rabbits

At least 5 days before induction of hypertension, mean arterial pressure, plasma volume, extracellular fluid volume, plasma sodium, plasma potassium, hematocrit, daily water intake, urine output (UO) and water balance were determined in the conscious rabbits. Five days of daily fluid/electrolyte measures were then obtained, after which a second series of control cardiovascular and fluid volume measurements were performed.

Induction of Hypertension in Normotensive Rabbits

The induction for hypertension was done by following methods: Subcutaneous injection of methyl prednisolone acetate (20 mg/Kg/week). Two weeks later, rabbits with a minimum mean BP of 150 mmHg were selected. This method has been used for studies of Ca ++ Channel blockers ad Angiotensin related antihypertensive drugs.

Measurement of other parameters in Hypertensive Rabbits

After induction of hypertension, mean arterial pressure, plasma volume, extracellular fluid volume, plasma sodium, plasma potassium, hematocrit, daily water intake, urine output (UO) and water balance were determined in the conscious rabbits.

Experimental Study Design

The rabbits used in study were divided into four groups:

Group I: Negative control. In this group 6 male rabbits were selected to serve as control group received no further treatment.

Group II: Amlodipin treated. In this group 6 male rabbits were selected to serve as control group received Amlodipin treatment.

Group III: Benzapril treated. In this group 6 male rabbits were selected to serve as control group received Benzapril treatment.

Group IV : Amlodipin + Benzapril treated. In this group 6 male rabbits were selected to evaluate the beneficial effect of combined therapy.[15]

The experimental Procedures for above groups were same as all parameters should be assessed to check effectiveness of therapy. After induction of hypertension, groups were subjected to treatment as per design. The Single layer films and bi layer films were administered to the animals of respective groups. The rabbits were then placed in the restrainer and different parameters were noted down.

Mean arterial pressure (MAP)

Mean arterial pressure (MAP) was measured using Non-invasive blood pressure apparatus (Biopac Systems, Inc Santa Barbara, USA). The restrainer carrying the animals was placed in the restrainer with tail protruding out. Systolic blood pressure was measured indirectly in conscious and slightly restrained rabbit by the tail cuff method. An average of five consecutive readings was noted.

Measurement of Other parameters

The other parameters like Plasma volume (PV), extra cellular fluid volume (ECFV), Hematocrit Value (Hct), Plasma sodium (PNa), plasma potassium (PK), Daily water intake (WI), urine output (UO) and Water balance (WB) were also estimated before and after studies. [16]

RESULTS AND DISCUSSION

Optimization of Films

Selection and Optimization of Film Forming Agents

Various concentration of both film forming agents were prepared in ten batches as MOF-I to MOF-X. The optimization of film forming agents was done on basis of General Appearance, Thickness and weight. Batch MOF-III seems to produce desired thickness and weight of individual film was around 120 mg so for double layer it will be around about 250 mg. The batch was found transparent too. Thickness of this batch also suitable bilayer fast disintegration oral films aimed about 150µm.The thickness of all Batches lies between 62±2 to 118±6 µm. The

result shows that as the concentration of film forming polymer increases, the thickness of films also increases. When thickness of films is less than it fails the folding endurance and thick films are not transparent in nature so MOF- III was selected as optimized concentration of film forming agents.

Selection and Optimization of Plasticizer

The tensile strength of all batches (Except MOF- XIX and XX) was found to be 0.758 to 1.141 Kg/cm^2. This shows that all films having good tensile strength. The mechanical properties of the film were studied by percentage elongation which was found 22.6 to 62.3. The batch having highest % elongation and appropriate tensile strength was selected.

Hence batch MOF-XIII were optimized with selection of PEG-4000 due to better tensile strengths high flexibility (folding endurance).The results of this optimized batch were appropriate for envisaged oral film were as folding endurance 586±23, tensile strength 1.056 Kg/cm^2 and percentage elongation 62.3 were found.

Selection and Optimization of Super Disintegrants:

The concentration of super disinteresting agent/s were optimized on the basis of disintegration time.

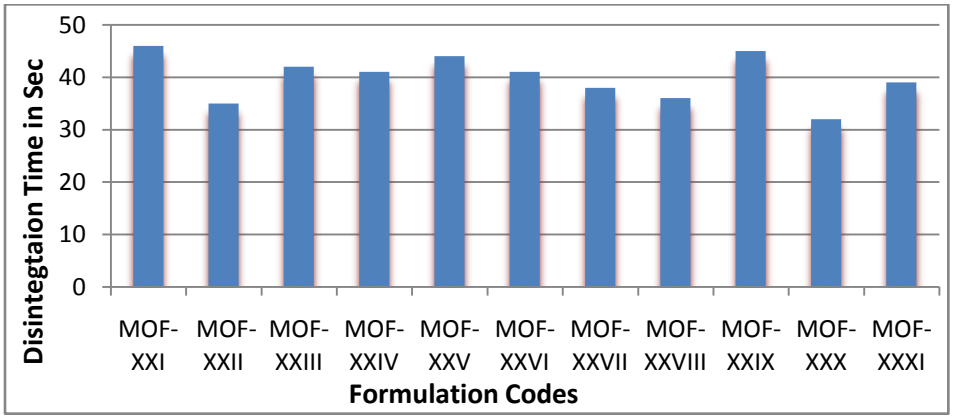

Figure. 2 Disintegration time of different batches

The disintegration time was found out in range of 32±1 to 46±2. The disintegration time decreases as concentration of super disintegrants increases. The Batch having least disintegration time was selected so as to get less dissolution time of drugs. A combination of SGS (250 mg) and Croscarmelose (50 mg) were able to disintegrate oral film within 32 seconds, Hence MOF-XXX were selected for further study.

Optimized Batches of Individual Films

Optimized batch of Amlodipine (ASOF-SI)

ASOF-SI (Amlodipine single layer oral film) was the optimized batch of Amlodipine 5mg.

ASOF-SI was able to disintegrate within 35 seconds with thickness of 79±5 µm. This single layered oral film was showing appropriate folding endurance (523±12), %-age elongation (46) and tensile strength (1.098 Kg/cm2).The weight of each film were 125±2 mg.

Optimized batch of Benazapril (BSOF-SI)

BSOF-SI (Benazapril single layer oral film) was the optimized batch of Benazapril 10mg. BSOF-SI was able to disintegrate within 33 seconds with thickness of 86±4 µ m. This single layered oral film was showing appropriate folding endurance (565±11), %-age elongation (53) and tensile strength (1.214 Kg/cm2).The weight of each film were 131±2 mg.

Characterization of Amlodipine and benazapril Bi Layer Fast Dissolving Films (AB-BFDOF)

Determination of Thickness

The Thickness of Bilayer film was determined from three different positions.

Table 1: Thickness of Bilayer film

S.NO.	Formulation Code	Thickness in µm
1	AB- BFDOF	183±4

The result shows that the thickness of Bilayer films was addition of thicknesses of two individual films and impermeable membrane. So there is no loss of thickness during process of joining of two layers.

Size of Films

The Size of films was cut as per unit dose of drug. The total size of film is around 80 x 20 cm and film cut in size of 2.0 x 1.5 cm as per unit dose of BFDOF.

Disintegration Time

The Disintegration time of Bilayer films was determined.

Table 2: Disintegration time of Bilayer film

S.No.	Formulation Code	Disintegration time in Sec
1	AB- BFDOF	53±3

The disintegration time was found out 53±3 sec. The disintegration time of Bilayer film was more than individual films. This may be due to impermeable membrane.

Tensile Strength and % Elongation Determination

The tensile testing gives an indication of the strength and elasticity of the film, reflected by the parameters - tensile strength, elastic modulus, % strain, and load at yield.

Table 3: Tensile Strength and %age elongation of Bilayer film

S.No.	Formulation Code	Tensile strength in Kg/cm^2	% elongation
1	AB- BFDOF	1.683	36

The tensile strength of Bilayer film was found to be 1.683 Kg/cm2. The tensile strength of Bilayer film was more than individual films as thickness of films was more than individual films. This shows that all films having good tensile strength. The mechanical properties of the film were studied by % elongation which was found 36. The % elongations of all films were satisfactory.

Folding Endurance

This test was performed by cutting the mouth dissolving film of size 3 x 2 cm^2. The films were folded at same place until it breaks apart**.**

Table 4: Folding Endurance of Bilayer film

S.No.	Formulation Code	Folding endurance
1	AB- BFDOF	458±10

Drug Content

The Drug Content of Bilayer film was determined from three different positions.

Table 5: Drug Content of Bilayer film

S.No.	Formulation Code	% Drug Content	
1	AB- BFDOF	**Amlodipine**	99.3±0.3
		Benazapril	98.9±0.6

The % drug content is similar to that of individual films which shows that their was no drug loss during fabrication of Bilayer film.

In *Vitro* Dissolution Studies

The dissolution studies of Bilayer film were performed at salivary pH for 60 min.

The dissolution data revealed that Bilayer film release both drugs within 1 hour and release were constant after 30-40 min which shows the release of drug from film is fast.

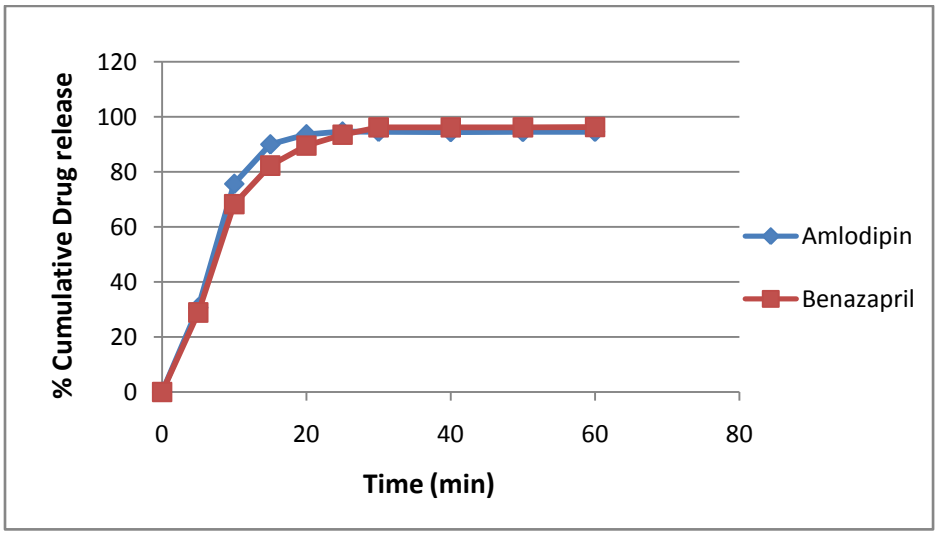

Figure. 3 Release profile of Amlodipin & Benzapril from Bilayer film

Stability testing

Table 6: Effect on Tensile Strength of Films

S. No.	Batch Code	@ 30^{0}C and 65%RH			@ 40^{0}C and 75 %RH		
		45 days	90 days	180 days	45 days	90 days	180 days
1.	AB-BFDOF	NC	NC	+0.12%	NC	+0.24%	+0.28%

Table .7: Effect on % Elongation of Film

S. No.	Batch Code	@ 30^{0}C and 65%RH			@ 40^{0}C and 75 %RH		
		45 days	90 days	180 days	45 days	90 days	180 days
1.	AB-BFDOF	NC	NC	+0.14%	+0.06%	+0.11%	+0.19%

Table 8: Effect on Disintegration time of Film

S. No.	Batch Code	@ 30^{0}C and 65%RH			@ 40^{0}C and 75 %RH		
		45 days	90 days	180 days	45 days	90 days	180 days
1.	AB-BFDOF	NC	NC	+0.12%	NC	+0.31%	+0.72%

Mean arterial pressure (MAP)

Systolic blood pressure was measured indirectly in conscious and slightly restrained, pre-warmed rat by the tail cuff method. An average of five consecutive readings was noted. The readings were recoded in Table.

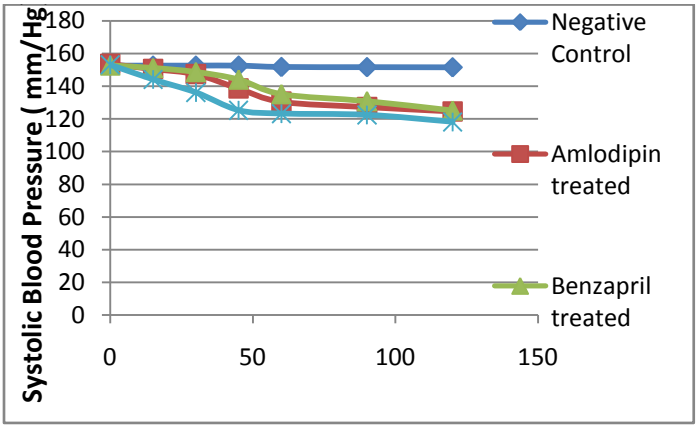

Figure. 5 Effect of oral film treatment on mean arterial pressure in rabbits

Plasma volume (PV) and extra cellular fluid volume (ECFV):

The plasma Volume and extracellular fluid volume was measured before inducing hypertension, after inducing hypertension and after treatment of rabbits. The readings are as follows:

Table 9: Effect of oral film treatment on volume and extra cellular fluid volume

S.No.	Stage of measurement	(PV) (ml/kg)	(ECFV) (ml/kg)
1	Before inducing hypertension	50	260
2	After inducing hypertension	70	290
3	After Treatment (Amlodipine)	55	265
4	After Treatment (Benzapril)	56	268
5	After Treatment (Amlodipin + Benzapril)	50	260

The plasma and extra cellular fluid volume was increased after induction of hypertension and again decreased to normal level after treatment.

Hematocrit Value

The Hematocrit was measured before inducing hypertension, after inducing hypertension and after treatment of rabbits. The readings are as follows:

Table 10: Effect of oral film treatment on Hematocrit Value

S.No.	Stage of measurement	Hematocrit Value (%)
1	Before inducing hypertension	40
2	After inducing hypertension	30
3	After Treatment (Amlodipine)	33
4	After Treatment (Benzapril)	32
5	After Treatment (Amlodipin + Benzapril)	40

The Hematocrit was decreased after induction of hypertension and again increased to less than normal level after treatment. This may be due to repeated blood sampling.

Plasma Sodium (PNa) and Plasma Potassium (PK)

The plasma Volume and extracellular fluid volume was measured before inducing hypertension, after inducing hypertension and after treatment of rabbits. The readings are as follows:

Table 11: Effect of oral film treatment on Plasma Sodium and Plasma Potassium

S.No.	Stage of measurement	Plasma Sodium (PNa) (mEq/l)	Plasma Potassium (PK)(mEq/l)
1	Before inducing hypertension	145	40
2	After inducing hypertension	130	30
3	After Treatment (Amlodipine)	138	36
4	After Treatment (Benzapril)	136	35
5	After Treatment (Amlodipin + Benzapril)	142	39

The plasma Sodium and Plasma Potassium was decreased after induction of hypertension and again increased to normal level after treatment.

Daily water intake (WI) and urine output (UO):

The plasma Volume and extracellular fluid volume was measured before inducing hypertension, after inducing hypertension and after treatment of rabbits. The readings are as follows:

Table 12: Effect of oral film treatment on Daily water intake and urine output

S.No.	Stage of measurement	Water Intake (ml/Day)	Urine Output (ml/Day)
1	Before inducing hypertension	300	175
2	After inducing hypertension	500	350
3	After Treatment (Amlodipine)	340	225
4	After Treatment (Benzapril)	335	220
5	After Treatment (Amlodipin + Benzapril)	310	180

The Water Intake and Urine output was increased after induction of hypertension and again decreased to close to normal level after treatment.

CONCLUSION

The data of all parameters shows that after treatment all parameter attain their normal value and as such no major variation was observed during experimentation.

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