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### FORMULATION AND DEVELOPMENT OF STABLE DOSAGE FORM OF AMLODIPINE BESYALTE AND BENAZEPRIL HYDROCHLORIDE TO OVERCOME PHYSICAL INCOMPATIBILITY

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#### ABSTRACT

Amlodipine is a dihydropyridine calcium channel blocker with a slow onset and long duration of action. Benazepril hydrochloride is an angiotensin- converting enzyme inhibitor. But the Amlodipine besylate and Benazepril are physically incompatible drugs so there is need to keep them physically separated in dosage form. There are various approaches to overcome incompatibility. Among which the bilayer tablet is one of the novel, suitable approach and increasing attention from a variety of industries for various reasons viz. The purpose of this research is to study the physical incompatibility between Amlodipine and Benazepril, to formulate and develop the dosage form that overcome the incompatibility. The incompatibility study was carried by mixing two drugs in 1:1 and 1:2 ratio and then stored at  $40^{\circ}\text{C} \pm 0.2^{\circ}\text{C}$  and relative humidity  $75\% \pm 0.5\%$ . The samples were examined for physical changes, pH, and IR studies at particular time of intervals. Photographs of samples are taken at particular interval. From incompatibility study it was concluded that the bilayer tablet is the suitable approach to overcome the incompatibility. In the bilayer tablets physical separation is achieved by coating the Benazepril hydrochloride granules with the gelatin and then formulating bilayer tablets to minimize contact between Amlodipine besylate and Benazepril hydrochloride leads to overcome physical incompatibility. Tablets were prepared by direct compression. A  $3^2$  Full factorial design was employed to systematically optimize the drug release profile, hardness and disintegration time. The stability study conducted for optimized formulation is stable having no impact on physical incompatibility.

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## INTRODUCTION [1- 3]

Drug Incompatibility refers to interactions between two or more substances which lead to changes in chemical, physical, therapeutic properties of the pharmaceutical dosage form. The undesirable results may be the consequence of the interaction between formulations ingredients of the products formed due to these interactions.

### Types of Drug Incompatibility

1. Physical incompatibility
2. Therapeutic incompatibility
3. Chemical incompatibility

In the treatment of hypertension, combination therapy is important because antihypertensive monotherapy is effective in only 40% of patients worldwide. Amlodipine is a calcium channel blocker with a slow onset of action and long duration of action. Benazepril hydrochloride an angiotensin- converting enzyme inhibitor. But this combination is physically incompatible. It is therefore the principal object of the research to prepare a stable pharmaceutical dosage form of Amlodipine besylate and Benazepril hydrochloride design in that the two drugs are not physically contact with each other.

From above problem we come to know that bilayer tablet is the most suitable approach to avoid physical and chemical incompatibility between drugs. Bi-layer tablets can be a primary option to avoid physical incompatibilities between drugs by physical separation. Bilayer tablet is improved beneficial technology to overcome the shortcoming of the single layered tablet. The objective of the dosage form is to ensure that the drugs available to its citizen are not only safe and effective, but are also properly manufactured and packaged to meet the established quality target product profile over its shelf life.

In the present research physical separation is achieved by coating one drug (Benazepril hydrochloride) with the gelatin and then formulating the bilayer with the coated granules in one layer with excipients and second layer contains Amlodipine besylate with desired excipients.[4]

### ADVANTAGES OF THE BILAYER TABLET DOSAGE FORM <sup>[2]</sup>

1. Bi-layer execution with optional single-layer conversion kit.
2. Cost is lower compared to all other oral dosage form
3. Greatest chemical and microbial stability over all oral dosage form.
4. Objectionable odour and bitter taste can be masked by coating technique.
5. Flexible Concept.
6. They are unit dosage form and offer the greatest capabilities of all oral dosage form for the greatest dose precision and the least content variability.
7. Easy to swallowing with least tendency for hang up.
8. Suitable for large scale production.

### DISADVANTAGES OF BILAYER TABLET DOSAGE FORM <sup>[2]</sup>

1. Some drugs resist compression into dense compacts, owing to amorphous nature, low density character.
2. Bitter tasting drugs, drugs with an objectionable odour or drugs that are sensitive to oxygen may require encapsulation or coating.
3. Difficult to swallow in case of children and unconscious patients.
4. Drugs with poor wetting, slow dissolution properties, optimum absorption high in GIT may be difficult to formulate or manufacture as a tablet that will still provide adequate or full drug bioavailability.

### MATERIALS AND METHOD:

Drug: 1. Amlodipine besylate

2. Benazepril hydrochloride

Excipients: 1. Croscopollose

2. Microcrystalline cellulose

3. Mannitol

4. Starch

5. Lactose monohydrate

6. Sodium starch Glycolate

7. Magnesium stearate

### Procurement of Drugs and Excipients:

1. Amlodipine besylate was obtained as gift sample from Glenmark Pharmaceuticals, Goa.

2. Benazepril hydrochloride was obtained as gift sample from Wockhardt pharmaceuticals, Aurangabad.

Excipients used were of Analytical grade and obtained from college laboratory, Nashik.

### METHOD:

Tablets were prepared by direct compression. Previously both the blends prepared separately. Amlodipine layer was compressed at low compression force by using 9 mm punch with the minimum hardness. Benazepril layer was placed on compressed layer of amlodipine which was double compressed to form bilayer tablets with desired hardness.

**EXPERIMENTAL:****Preformulation study:****a. Organoleptic properties:**

The sample of Amlodipine besylate and Benazepril hydrochloride were studied for organoleptic properties such as color, odor and appearance.

**b. Melting point:**

Melting point was determined by open capillary method using melting point apparatus.

**c. Determination of solubility**

Saturation solubility of Amlodipine besylate and Benazepril hydrochloride were determined in Water and 0.1 N HCl.

**d. UV spectroscopy (Determination of  $\lambda_{\max}$ )**

Stock solution (100  $\mu\text{g/ml}$ ) of Amlodipine besylate and Benazepril hydrochloride were prepared in 0.01N HCL and methanol. This solution was appropriately diluted with respective solvents to obtain suitable concentrations ( $\mu\text{g/ml}$ ). The UV spectrum was recorded in the range of 200-400 nm by using UV Visible Spectrophotometer.

**Compatibility study of drug with excipients:****a. IR Spectroscopy:**

The FTIR spectrum of Amlodipine besylate and Benazepril hydrochloride and physical mixture with the excipient were recorded using FTIR spectrophotometer.

**b. Differential scanning calorimetric (DSC) studies:**

Thermal analysis was performed using a differential scanning calorimeter equipped with a computerized data station. The sample of pure drug, and physical mixture were heated at a scanning rate of  $10^\circ\text{C}/\text{min}$  between 30 and  $350^\circ\text{C}$  and 40 ml/min of nitrogen flow. The differential scanning calorimetry analysis gives an idea about the interaction of various materials at different temperature. It also allows us to study the possible degradation of the material.

**INCOMPATIBILITY STUDY:**

The incompatibility study between two drugs amlodipine besylate and Benazepril hydrochloride were carried by mixing the two drugs in 1:1 and 1:2 ratio and these mixture is then stored at  $40^\circ\text{C} \pm 0.2^\circ\text{C}$  and relative humidity  $75\% \pm 0.5\%$ . the samples were examined for physical changes, Ph, and IR studies at particular time of intervals. Photographs of samples are taken at particular interval.

**FORMULATION AND DEVELOPMENT:****Preformulation:**

When mixture of uncoated granules of Benazepril with formulation blend are stored at  $40^\circ\text{C} \pm 0.2^\circ\text{C}$  and relative humidity  $75\% \pm 0.5\%$ . the mixture shows development of yellow color which is due to incompatibility between two drugs. But when the Benazepril granules are coated with the gelatin and then the mixture of coated granules of Benazepril, amlodipine with excipients are stored at same storage conditions the physical contact is minimised due to coating and the incompatibility can be reduced.

**Preliminary trials:**

The preliminary study is based on the minimization of contact between the Amlodipine besylate and Benazepril hydrochloride.

Remedy: Need for physical separation

1. Reduction of area of contact (by granulation of one drug)
2. Reduction of area by layering (Bilayer tablets)
3. Physical separation of two drugs (by coating one drug and formulating bilayer tablets)

**Benazepril hydrochloride Granules preparation:**

**Table.1. Trial batches of Benazepril granules.**

Sr no	Trial 1	Qty (mg)	Trial 2	Qty (mg)
1	Benazepril hydrochloride	10	Benazepril hydrochloride	10
2	Mannitol	30	Lactose monohydrate	54
3	Crosspovidone	4.0	Pregelatinized starch	4.5
4	Ethyl cellulose	0.2	Purified water	Q.S.
5	Ethanol	Q.S.		

From the above trial batches the 2<sup>nd</sup> batch is selected for further formulation.

Coating of granules: The prepared Benazepril granules are coated with the 5% solution of gelatin.

**COMPOSITION OF TRAIL BATCHES:**

<b>Trail 1 (single layer tablet with granules of one drug)</b>		<b>Trail 2 (bilayer tablet with granulation of one drug)</b>		<b>Trail 3 (bilayer tablet with coating of one drug with gelatin)</b>	
Ingredients	Qty (mg)	Ingredients	Qty (mg)	Ingredients	Qty(mg)
Amlodipine besylate	5	Amlodipine besylate	5	Amlodipine besylate	5
Mannitol	60	Starch	6	Starch	6
Crosspovidone	15	Crosspovidone	7	Crosspovidone	7
Starch	15	Mannitol	60	Mannitol	60
Sodium starch glycolate	12	MCC	67	MCC	67
MCC	78	Magnesium stearate	5	Magnesium stearate	5
Benazepril hydrochloride granules	10	Benazepril hydrochloride granules	10	Benazepril hydrochloride granules (gelatin coated)	10
Magnesium stearate	5	Crosspovidone	12	Crosspovidone	12
-		Starch	8	Starch	8
-		MCC	105	MCC	105
-		Magnesium stearate	5	Magnesium stearate	5

**Optimisation:**

Based on the incompatibility study and the preliminary trials, 3<sup>2</sup> randomized full factorial design was applied in present study. In this design 2 factors were evaluated at 3 levels and experimental trials were performed at all 9 possible combination. The Crosspovidone(X<sub>1</sub>) and polyvinyl pyrrolidone (X<sub>2</sub>), were selected as independent variables. % Drug release, Disintegration time and hardness, were selected as dependent variables. The resulting data were fitted into design expert software and analysed statically using analysis of variance (ANOVA).

**Formulation batches using 3<sup>2</sup> factorial designs.****Amlodipine layer:****Table 3. Formulation batches using 3<sup>2</sup> Factorial design.**

Ingredients	F1(mg)	F2(mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)
Amlodipine besylate	5	5	5	5	5	5	5	5	5
Crosspovidone	9	8	7	9	7	8	9	8	7
Starch	6	7	6	8	8	6	7	8	7
Mannitol	40	40	40	40	40	40	40	40	40
Microcrystalline cellulose	85	85	87	83	85	86	84	84	86
Magnesium stearate	5	5	5	5	5	5	5	5	5
Final weight	150	150	150	150	150	150	150	150	150

**Benazepril hydrochloride:****Table 4. Formulation batches using 3<sup>2</sup> Factorial design.**

Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)
Benazepril hydrochloride	10	10	10	10	10	10	10	10	10
Lactose	54.5	54.5	54.5	54.5	54.5	54.5	54.5	54.5	54.5
Starch	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5
Water	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Starch	6	7	6	8	8	6	7	8	7
Crosspovidone	9	8	7	9	7	8	9	8	7
MCC	61	61	63	59	61	62	60	60	62
Mg stearate	5	5	5	5	5	5	5	5	5
Final weight	150	150	150	150	150	150	150	150	150

**STABILITY STUDIES:**

In any rational design and evaluation of dosage forms for drugs, the stability of the active component is a major criterion in determining their acceptance or rejection

**Storage Condition: 40°C ± 2°C/ 75%RH ± 5% RH**

**RESULT AND DISCUSSION:**

Preformulation Studies

Organoleptic Properties:

**Table 5. Comparison of results of identification test of Amlodipine besylate and Benazepril hydrochloride with the reported standards.**

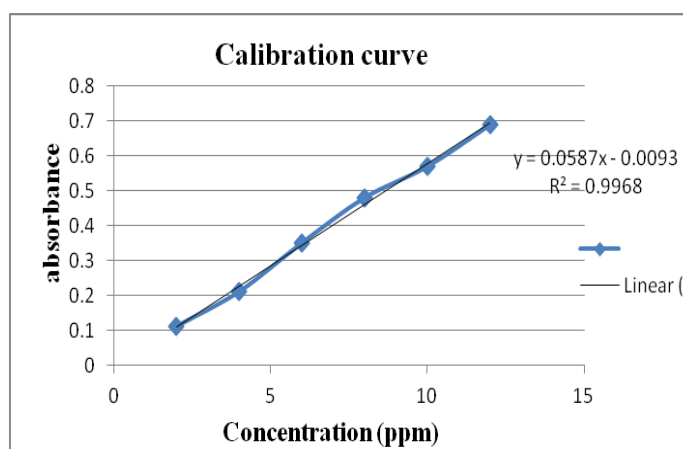
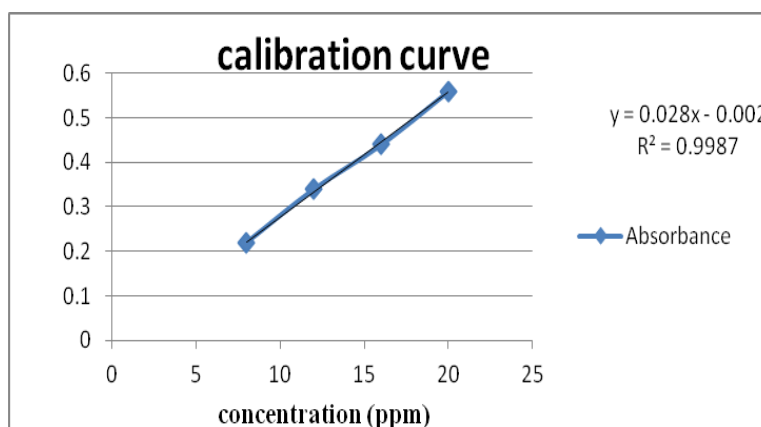
Sr. No	Organoleptic Properties	Amlodipine besylate		Benazepril hydrochloride	
		Observed	Reported	Observed	Reported
1.	Colour	White	White	White	White
2.	Odour	Characteristic	Characteristic	Characteristic	Characteristic
3.	Appearance	Crystalline	Crystalline powder	Crystalline	Crystalline
4.	Melting point	195-204° C	196 <sup>0</sup> C - 206 <sup>0</sup> C	180°C - 190°C	183°C - 192°C

**Determination of Solubility:****Table 6. Solubility of Amlodipine besylate and Benazepril hydrochloride.**

Sr no.	Solvent	Solubility	
		Amlodipine besylate	Benazepril hydrochloride
1	Water	75.3 mg/L	5 mg/Ml
2	0.01 N HCl	0.0035 mg/ml	0.0181 mg/ml

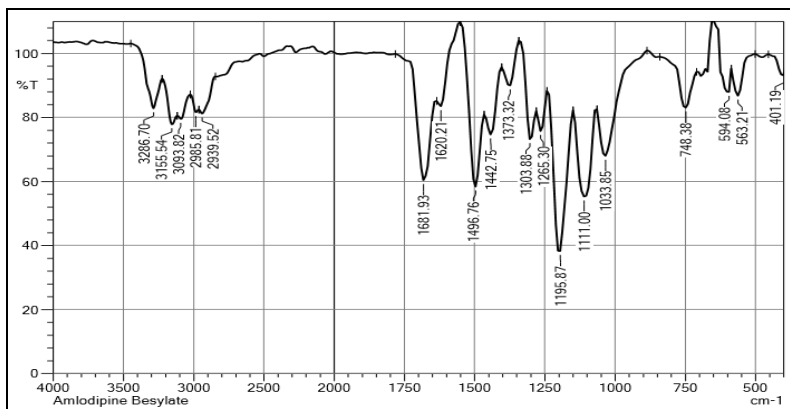
**UV Spectroscopy:**

Amlodipine Besylate

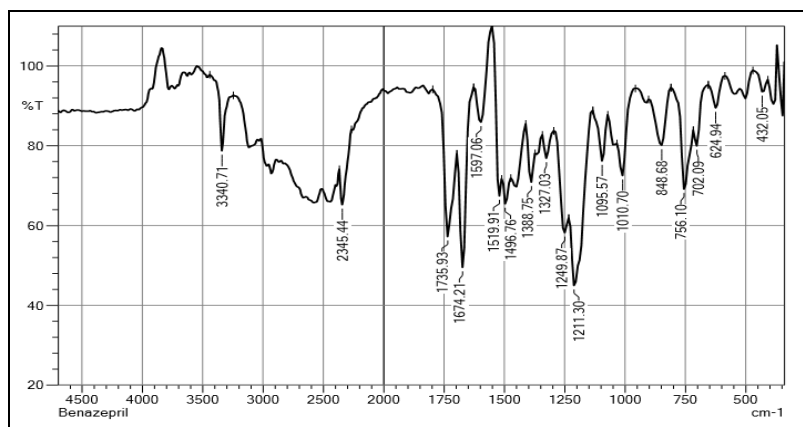
**Fig 1. Beer-lamberts plot of Amlodipine besylate in 0.01N HCL.****Benazepril Hydrochloride****Fig 2. Beer-lamberts plot of Benazepril hydrochloride in 0.01 N HCL.**

**IR Spectra:**

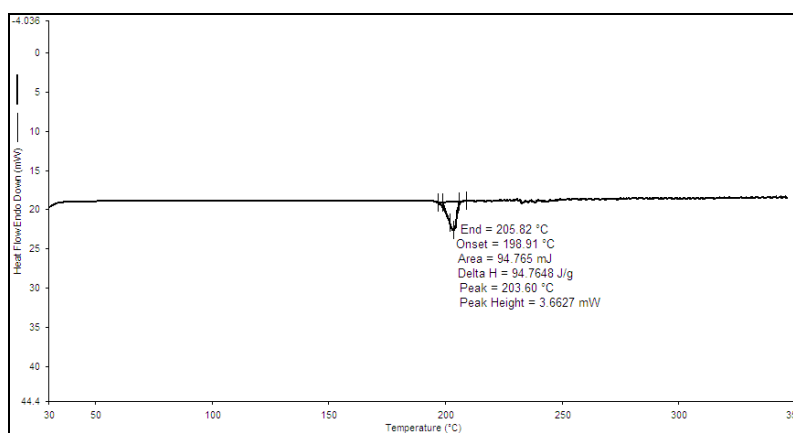
Amlodipine besylate:

**Fig 3. FTIR Spectrum of Amlodipine besylate.**

Benazepril hydrochloride:

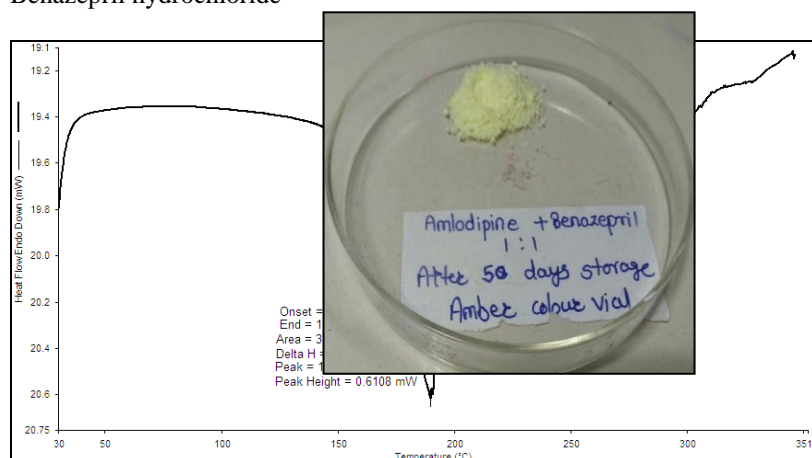
**Fig 4. FTIR Spectrum of Benazepril hydrochloride.****DSC STUDY:**

Amlodipine besylate:

**Fig 5. DSC Thermogram of Pure Amlodipine besylate.**



## Benazepril hydrochloride



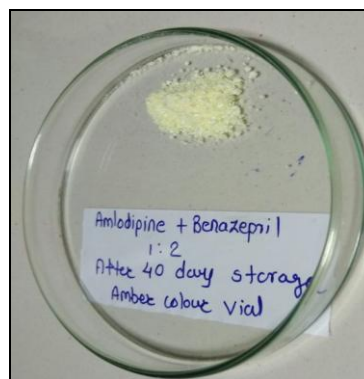
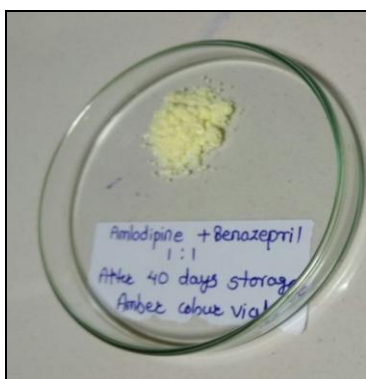
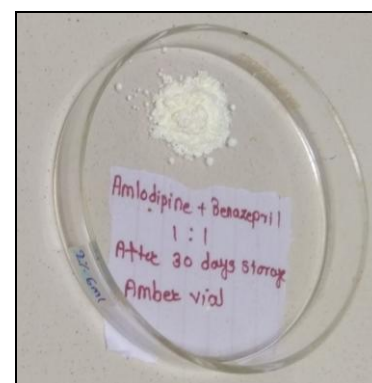
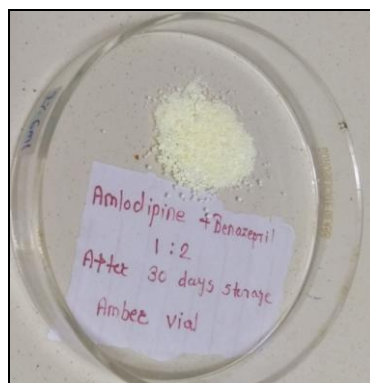
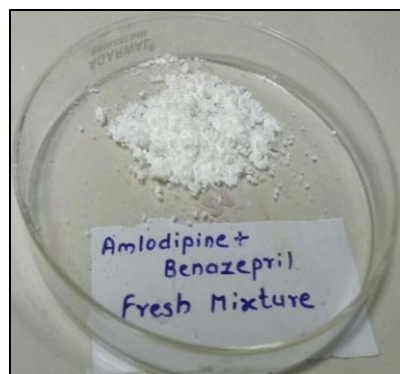
**Fig 6. DSC Thermogram of Pure Benazepril hydrochloride.**

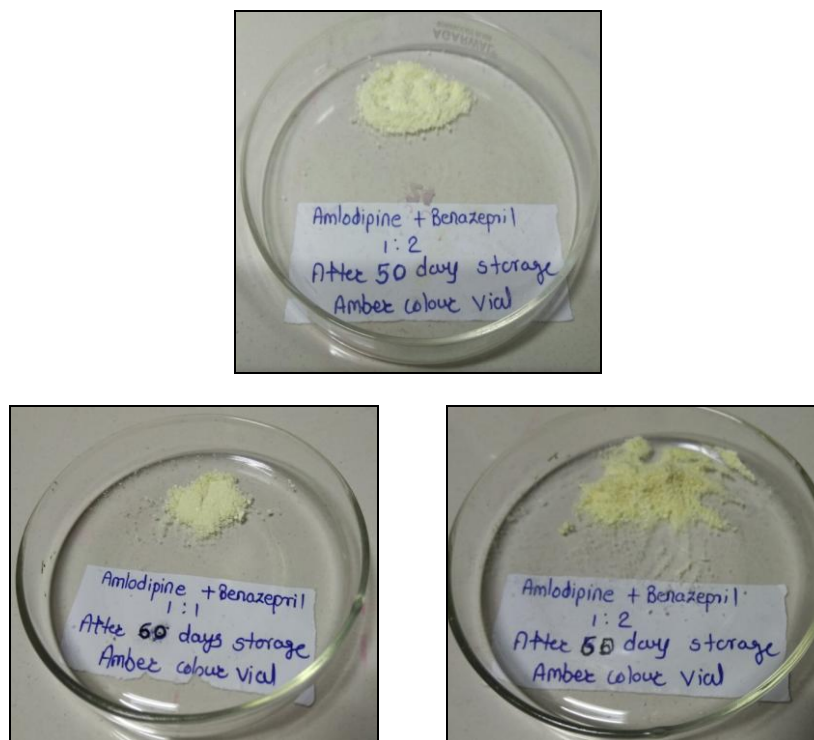
DSC of pure Amlodipine besylate showed a sharp endothermic peak at 203°C which is associated with the melting point of drug. Benazepril hydrochloride showed a sharp endothermic peak 189°C which is associated with the melting point of drug.

### INCOMPATIBILITY STUDY:

The Amlodipine besylate and Benazepril hydrochloride are physically incompatible drugs. There incompatibility study were carried out by mixing two drugs at 40 °C  $\pm$  0.5°C, and relative humidity 75%  $\pm$  0.2%. The observations are as follows.

Photographs of samples at intervals:





**Fig 7. Photographs of incompatibility studies at time interval.**

From the photographs of particular interval it is concluded that due to the physical incompatibility between two drugs there is color change from white to pale yellow followed by dark yellow.

#### pH study:

**Table 7. pH study of incompatible sample.**

Days	A+B (1:1) amber color vial	A+B (1:2) amber color vial
Fresh mix	4.45	2.84
25	7.63	6.99
30	8.01	7.99
35	6.5	6.6
40	6.5	6.65
45	6.52	6.40
50	6.89	6.68
55	6.89	7.09
60	6.90	7.09
65	6.95	7.12
90	7.02	7.10

From the literature it is found that if pH of microenvironment is above 5 the composition shows incompatibility. In the study of pH at particular time intervals increased pH was observed which proves that both drugs are incompatible with each other.

#### IR study:

Fresh physical mixture of both drugs.



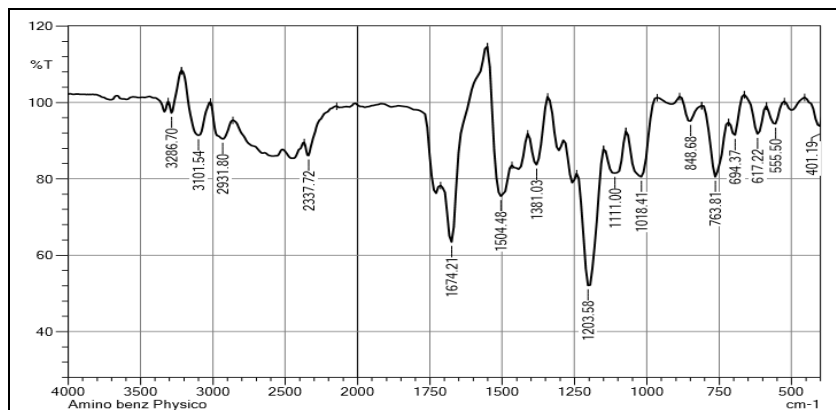


Fig 8. FTIR Spectra of Amlodipine and Benazepril physical mixture.

Storage after 15 days :

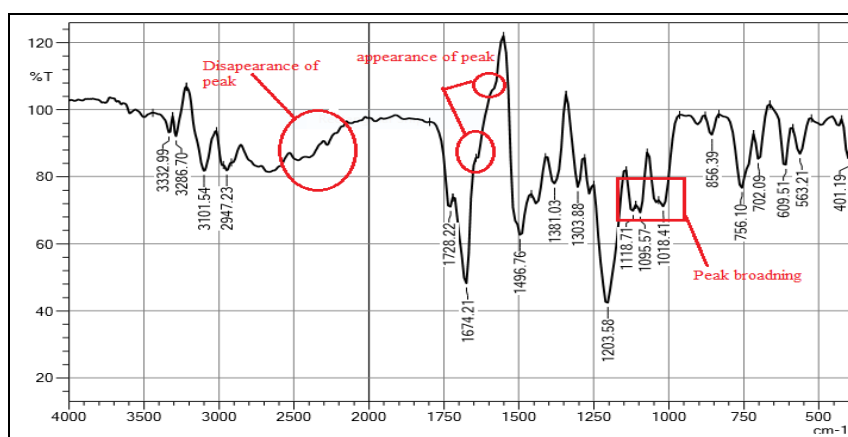


Fig 9. FTIR spectra of Amlodipine and Benazepril after 15 days storage.

C Storage after 1 month:

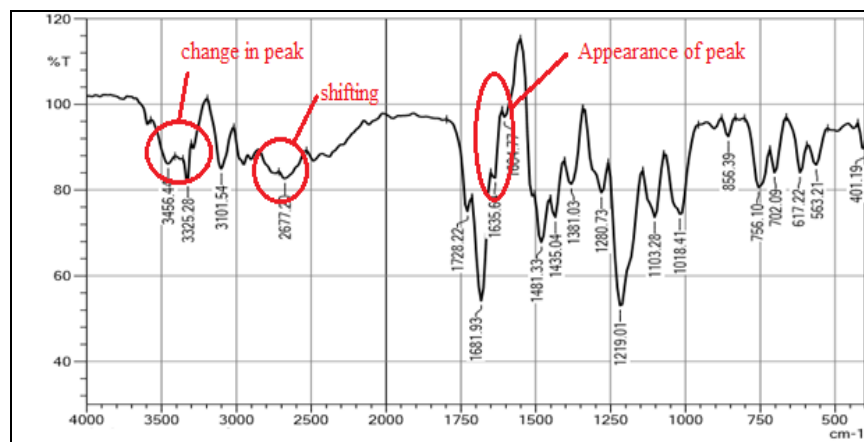
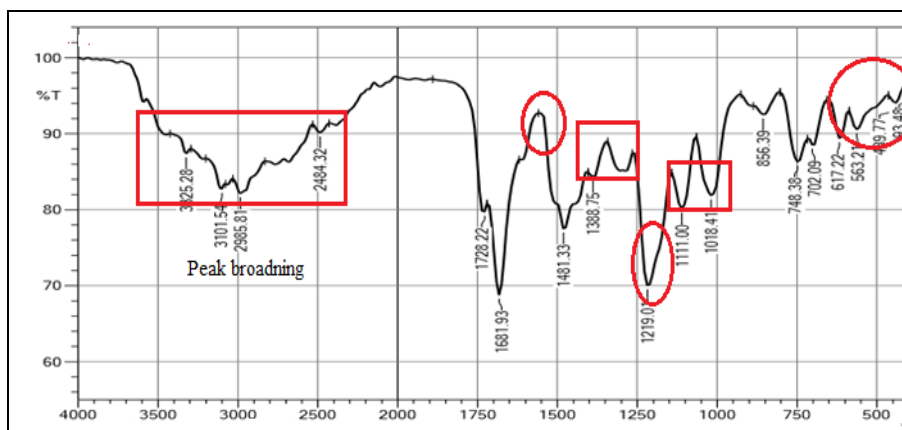
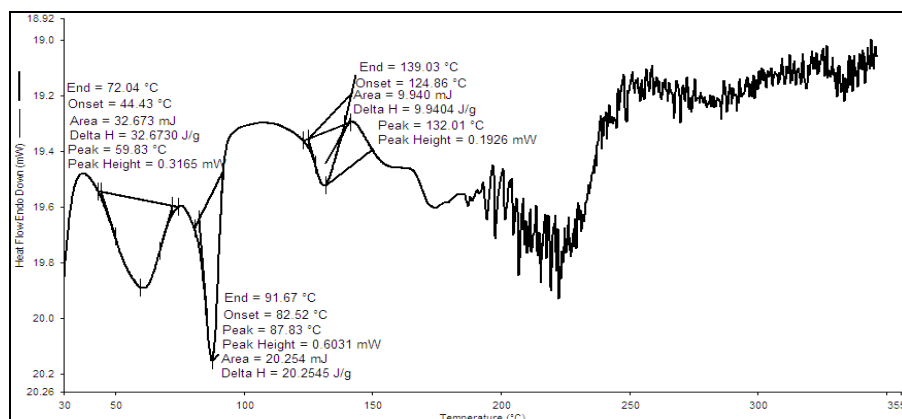


Fig 10. FTIR spectra of Amlodipine and Benazepril after 30 days storage.

**Storage after 3 months:**

**Fig 11. FTIR Spectra of Amlodipine and Benazepril mixture after 3 month storage.**

As time interval increases intensity of peak and sharpness was decreased. There is change in the peak was observed.

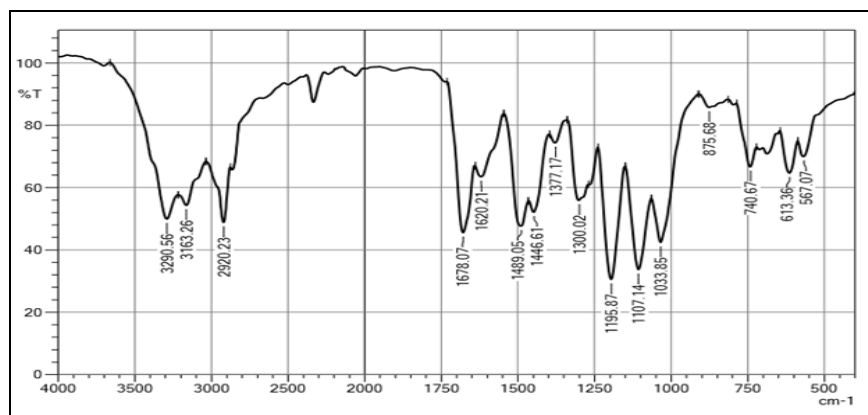
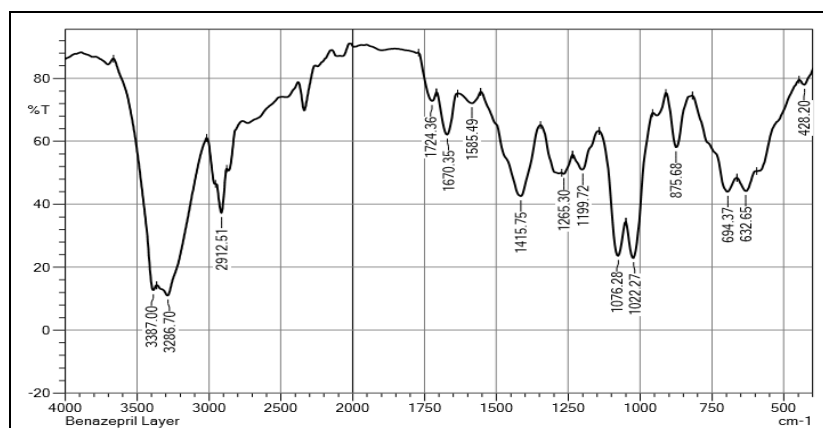
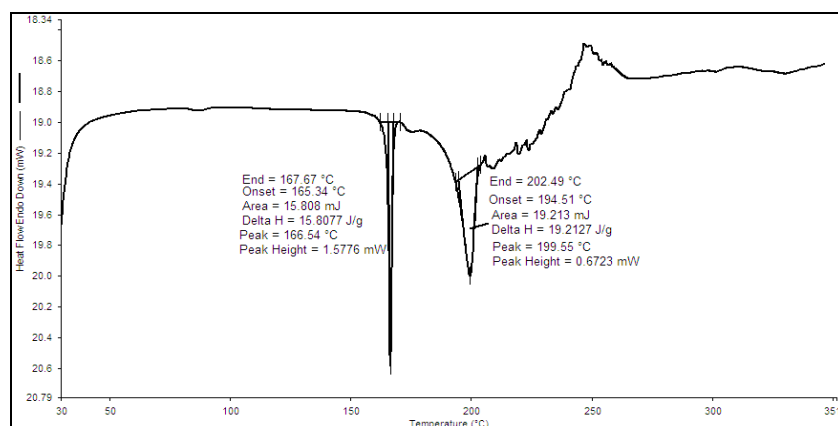
**DSC STUDY:**

**Fig 12. DSC Thermogram of Physical mixture of Amlodipine besylate and Benazepril hydrochloride.**

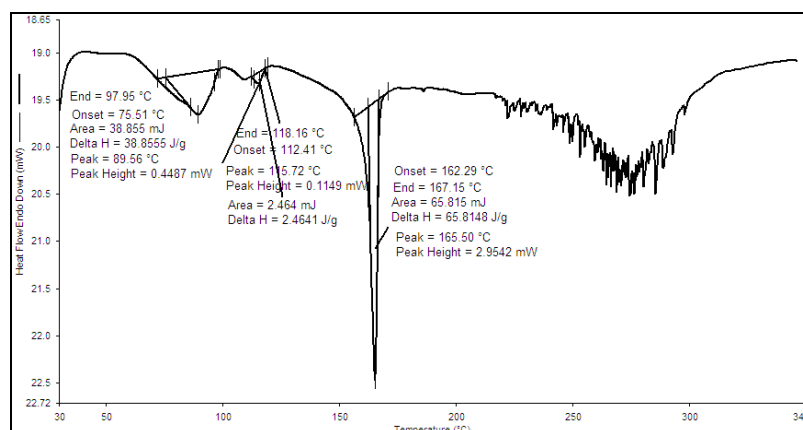
When the mixture of Amlodipine and Benazepril mixture was stored at it was conclude that  $40^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$ , and relative humidity  $75\% \pm 0.2\%$  for 2 months and then DSC Thermogram was recorded. It shows change in endothermic peak of Amlodipine and Benazepril which were observed in single Thermogram of both the drugs. It proves that both the drugs are incompatible with each other.

**Drug Excipient Compatibility study:****FTIR:**

Following figures shows the FTIR spectra's of Amlodipine besylate with added excipients and Benazepril hydrochloride with added excipients. The FTIR spectra did not show any significant difference from those obtained for their physical mixture. These obtained results indicate that added excipients are compatible with drugs.

**Amlodipine besylate with excipients:****Fig 13. FTIR Spectra of Amlodipine besylate with added excipients.****Benazepril hydrochloride with excipients:****Fig 14. FTIR Spectra of Benazepril hydrochloride with added excipients.****DSC:****Amlodipine and added excipients:****Fig 15. DSC Thermogram of Amlodipine and added excipients.**

## Benazepril and added excipients:



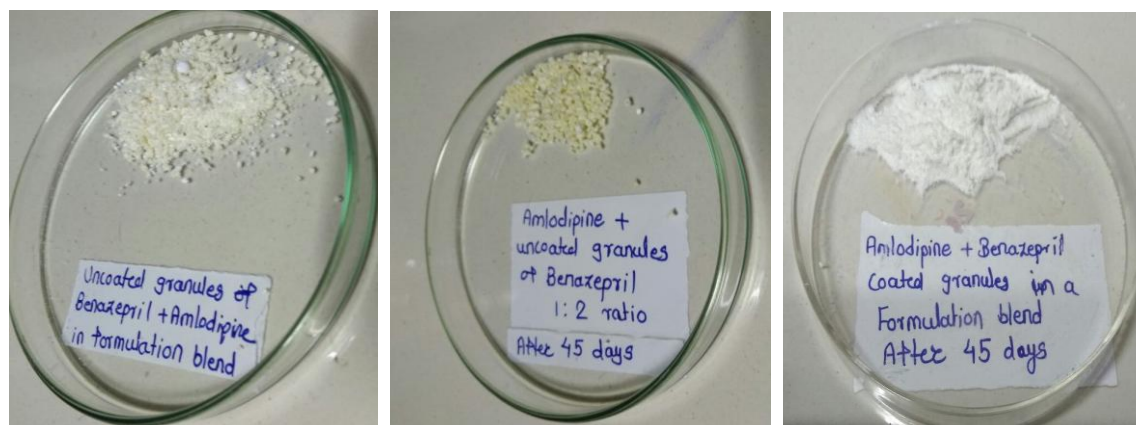
**Fig 16. DSC Thermogram of Benazepril and added excipients.**

Thermograms of pure Amlodipine and Amlodipine + added excipients are recorded. In the case of pure Amlodipine, a sharp endotherm was observed at 203°C, corresponding to the melting point of Amlodipine. While in case of Amlodipine + added excipients a sharp endotherm was observed at 199°C. Also in case of Benazepril, a sharp endotherm was observed at 189°C, corresponding to its melting point. While in case of Benazepril and added excipients a sharp endotherm was observed at 167°C. From these results it was concluded that both the drugs are compatible with excipients.

## FORMULATION AND DEVELOPMENT:

### Preformulation:

When mixture of uncoated granules of Benazepril with formulation blend are stored at 40 °C±0.2°C and relative humidity 75%±0.5%, the mixture shows development of yellow color which is due to incompatibility between two drugs. But when the Benazepril granules are coated with the gelatin and then the mixture of coated granules of Benazepril, amlodipine with excipients are stored at same storage conditions the physical contact is minimised due to coating and the incompatibility can be reduced.



**Fig 17. Preformulation study.**

Preliminary trials: The preliminary study is based on the minimization of contact between the Amlodipine besylate and Benazepril hydrochloride.

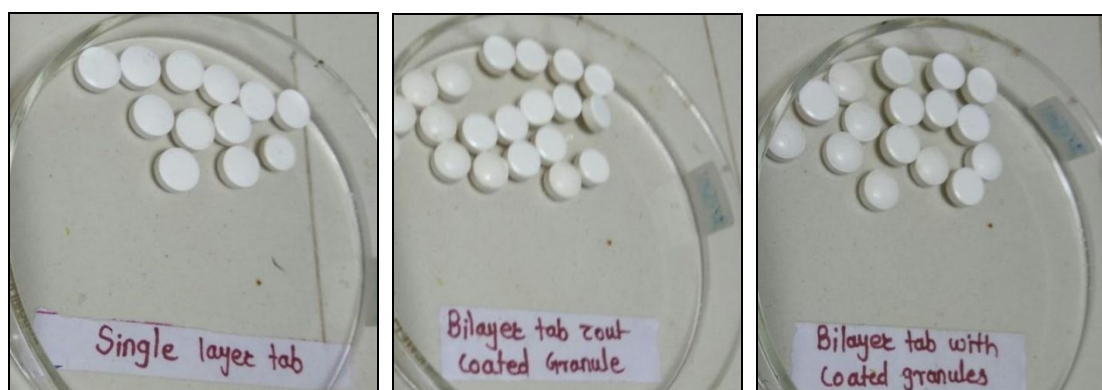
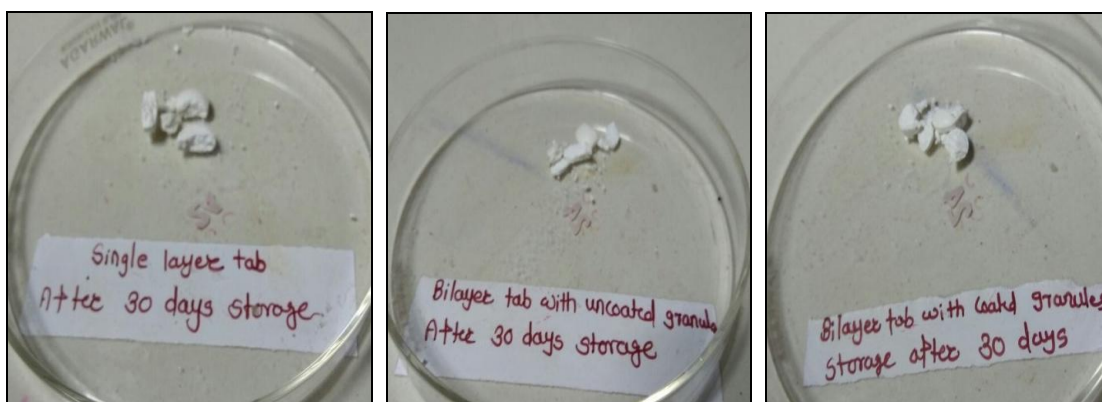
Remedy: Need for physical separation

- 1.Reduction of area of contact (by granulation of one drug)
- 2.Reduction of area by layering (Bilayer tablets)
- 3.Physical separation of two drugs (by coating one drug and formulating bilayer tablets)

**Benazepril hydrochloride Granules evaluation:****Table 8. Benazepril hydrochloride Granules evaluation.**

Formulation	Bulk density (gm/cm <sup>3</sup> )	Tapped density (gm/cm <sup>3</sup> )	Carr's index (%)	Hausner ratio	Angle of repose (°)
Benazepril hydrochloride granules	0.45	0.51	11.76	1.1	25.65

Coating of granules: The prepared Benazepril granules are coated with the 5% solution of gelatin

**Trail Batches:****Fig 18. Trail batches of tablets when prepared.****Fig 19. Tablets after 30 days storage.**

From the above photographs it was observed that the single layer tablet shows slightly yellow color after 30 days, and in case of bilayer tablet which contains uncoated granules of Benazepril just started to appear yellow. while in case of bilayer tablet with coated granules of Benazepril due to complete physical separation no yellow color was observed. That proves the bilayer tablet with coated granules of one drug gives better separation between two incompatible drugs.

**Evaluation of powder blend:**  
**Amlodipine besylate layer:**

**Table 9. Evaluation of Powder characteristics of Amlodipine besylate.**

Formulation	Bulk density (gm/cm <sup>3</sup> )	Tapped density (gm/cm <sup>3</sup> )	Carr's index (%)	Hausner ratio	Angle of repose (θ)
F1	0.40	0.50	20.00	1.25	25.64
F2	0.41	0.47	12.29	1.14	27.78
F3	0.41	0.50	18.24	1.21	29.30
F4	0.40	0.50	20.11	1.25	25.44
F5	0.43	0.51	15.68	1.09	26.13
F6	0.40	0.50	20.89	1.25	28.09
F7	0.41	0.50	18.11	1.21	25.55
F8	0.41	0.52	21.22	1.26	25.46
F9	0.43	0.55	21.81	1.22	25.26

**Benazepril hydrochloride layer:**

**Table 10. Evaluation of Powder characteristics of Benazepril hydrochloride.**

Formulation	Bulk density (gm/cm <sup>3</sup> )	Tapped density (gm/cm <sup>3</sup> )	Carr's index (%)	Hausner ratio	Angle of repose (θ)
F1	0.40	0.52	23.07	1.2	26.13
F2	0.38	0.45	15.55	1.09	25.69
F3	0.39	0.45	13.33	0.95	25.83
F4	0.40	0.48	16.66	1.12	28.49
F5	0.47	0.55	14.54	1.17	25.16
F6	0.43	0.48	10.11	0.95	26.92
F7	0.39	0.45	13.33	1.15	28.72
F8	0.40	0.52	23.07	1.23	25.30
F9	0.43	0.55	21.81	1.21	25.28

**Evaluation of Tablets:**

**Hardness:**

Hardness was found to be 5-6 kg/cm<sup>2</sup> which have good mechanical strength.

**Friability:**

Friability was found to be within the limits and was reported to be 0.64 %.

Weight variation: The average percentage deviation of 20 tablets of each formula was less than 7.5% which provide good uniformity.

**In vitro drug release study:**

**Amlodipine layer:**

**Table 11. Evaluation of tablet friability, hardness, thickness and Drug content.**

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
5	13.96	15.55	17.93	19.52	13.96	11.58	10	10.79	9.20
10	19.00	20.62	23.05	23.88	22.97	22.13	26.86	26.46	22.88
15	24.93	25.00	25.89	30.70	30.57	31.30	37.71	31.41	28.09
20	31.49	31.52	31.59	36.46	38.03	38.09	42.22	38.95	37.19
25	37.28	35.70	36.51	41.46	45.46	43.89	44.09	47.08	42.22
30	42.28	41.46	42.27	47.22	49.71	49.68	52.93	52.93	48.84
40	57.82	59.41	56.46	59.57	62.03	64.43	66.98	70.13	58.84
50	72.73	78.32	75.19	72.81	74.44	76.08	76.98	77.89	72.76
60	82.76	87.26	84.85	84.56	84.56	86.32	85.79	86.64	85.76



Table 12. % CDR of Amlodipine layer.

Formulation	Friability test	Hardness (kg/cm <sup>2</sup> )	Thickness (mm)	Drug content (%)	
				Amlodipine	Benazepril
F1	0.34	5.5	3.2	83.26	75.86
F2	0.5	5.6	3.2	86.53	83.08
F3	0.78	5.5	3.3	80.98	72.97
F4	0.92	5.6	3.2	80.19	79.83
F5	0.3	5.6	3.4	77.01	82.72
F6	0.4	5.5	3.0	81.77	79.11
F7	0.32	5.7	3.4	80.98	81.27
F8	0.9	5.6	3.3	84.44	82.72
F9	0.7	5.5	3.0	77.01	83.44

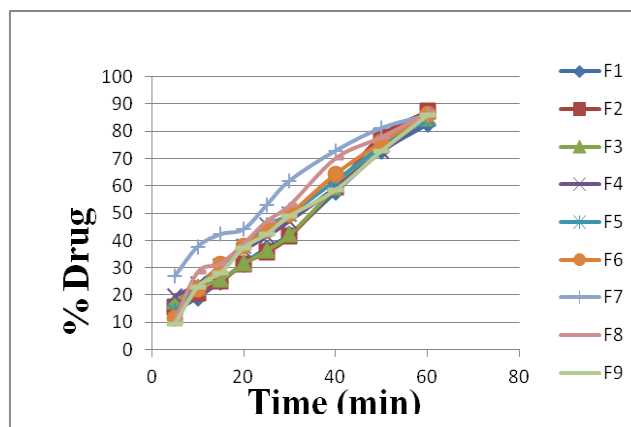


Fig 20. Dissolution profile of all formulations of Amlodipine layer.

Benazepril layer:

Fig 13. % CDR of Benazepril layer.

Time	F1	F2	F3	F4	F5	F6	F7	F8	F8
5	13.56	11.86	11.01	16.12	11.01	16.97	18.67	11.01	14.42
10	28.32	24.02	23.15	25.81	23.15	24.98	23.31	23.15	24.07
15	33.99	31.31	28.72	29.73	27.87	32.28	31.43	30.43	31.36
20	37.79	36.80	31.62	34.24	35.01	37.68	41.04	36.76	38.50
25	42.22	43.00	41.14	36.27	40.34	43.89	43.94	42.98	43.89
30	45.78	52.59	52.45	41.33	46.54	50.07	52.69	51.74	51.69
40	61.40	64.26	64.26	57.97	58.08	61.62	66.87	67.72	65.09
50	75.69	85.33	85.33	69.98	69.71	78.30	78.43	81.06	80.99
60	87.45	89.42	87.22	88.73	88.25	87.43	88.26	89.47	87.89

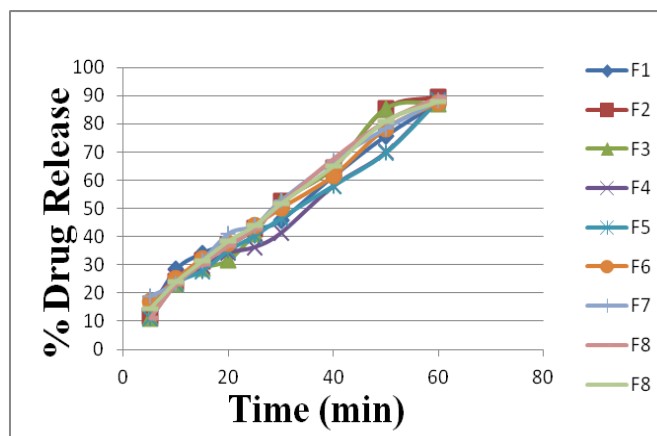


Fig 21. Dissolution profile of all formulations of Benazepril layer.

**Data Treatment:**

For Amlodipine besylate:

**Table 14. Drug release kinetics of Amlodipine layer.**

Formulation	Zero order	First order	Higuchi model	Hixon crowell	Korse-mayer peppas model	
	r <sup>2</sup>	r <sup>2</sup>	r <sup>2</sup>	r <sup>2</sup>	r <sup>2</sup>	N
F1	0.9942	0.5000	0.9500	0.9783	0.9766	1.15
F2	0.9797	0.5000	0.9928	0.9538	0.9544	1.16
F3	0.9718	0.4998	0.9150	0.9459	0.9290	1.16
F4	0.9977	0.5008	0.9681	0.9870	0.9686	1.18
F5	0.9953	0.5300	0.9927	0.9971	0.9993	1.18
F6	0.9948	0.5462	0.9905	0.9917	0.9975	1.17
F7	0.9637	0.5600	0.9791	0.9752	0.9545	1.19
F8	0.9809	0.5734	0.9709	0.9726	0.9661	1.19
F9	0.9846	0.5259	0.9948	0.9952	0.9070	1.18

For Benazepril hydrochloride:

**Table 15. Drug release kinetics of Benazepril layer.**

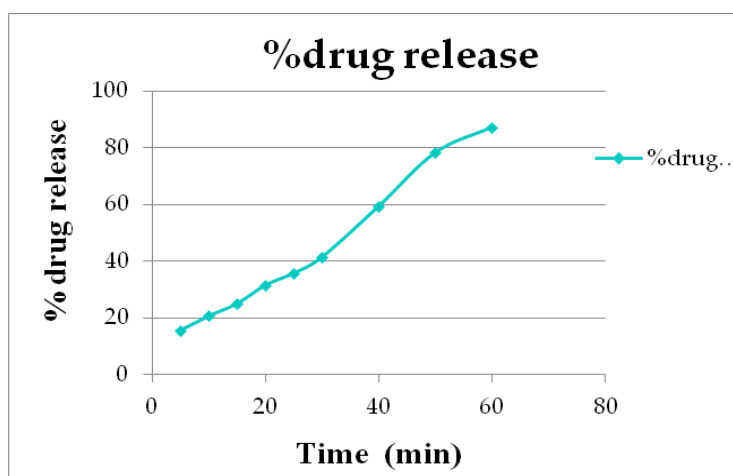
Formulation	Zero order	First order	Higuchi model	Hixon crowell	Korse-mayer peppas model	
	r <sup>2</sup>	r <sup>2</sup>	r <sup>2</sup>	r <sup>2</sup>	r <sup>2</sup>	n
F1	0.9543	0.5436	0.9600	0.9500	0.9630	1.18
F2	0.9931	0.6065	0.9879	0.9915	0.9929	1.19
F3	0.9865	0.6125	0.9631	0.9770	0.9831	1.17
F4	0.9689	0.5335	0.9373	0.9502	0.9660	1.16
F5	0.9918	0.5619	0.9899	0.9902	0.9945	1.16
F6	0.9989	0.5722	0.9862	0.9952	0.9948	1.19
F7	0.994	0.611	0.9660	0.9800	0.9700	1.20
F8	0.9945	0.6353	0.9782	0.9822	0.9930	1.18
F9	0.9981	0.6037	0.9855	0.9914	0.9979	1.19

**COMPOSITION OF OPTIMIZED FORMULATION:****Table 16. Composition of Optimized Formulation.**

Amlodipine layer	Qty (mg)	Benazepril layer	Qty (mg)
Amlodipine besylate	5	Benazepril hydrochloride	10
Crosspovidone	7.95	Lactose	54.5
Starch	6.84	Starch	4.5
Mannitol	40	Water	q.s
Microcrystalline cellulose	85.21	Starch	6.84
Magnesium stearate	5	Crosspovidone	7.95
Final weight	150	MCC	61.41
		Mg stearate	5
		Final weight	150

**In-vitro Release data:****Table 17. Percent Drug Release from Optimized Formulation.**

Sr. no	Time (min)	% drug release
1	5	15.55
2	10	20.62
3	15	25.00
4	20	31.52
5	25	35.70
6	30	41.46
7	40	59.41
8	60	87.26

**Fig 22. Dissolution profile of Optimized formulation.****Stability study:**

Storage condition:  $40^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$  & relative humidity  $75\% \pm 0.2\%$ .

**RESULTS****Table 18. Results of Stability Studies.**

Evaluation parameters	Results (Optimised batch)	
	1 Day	30 Day
Appearance	Concave, circular	Concave, circular
Thickness	3.5	3.5
Hardness	5.6	5.5
Disintegration time (sec)	116	115
In-vitro release (%)	87.26	86.58

**CONCLUSION**

- The Amlodipine besylate and Benazepril hydrochloride are physically incompatible with each other. When these two mixture store at  $40^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$  & relative humidity  $75\% \pm 0.2\%$  shows color change from white to yellow and increase in pH as the time interval increases also shows changes in FTIR spectra and DSC spectra.
- Due to changes observed in pH, FTIR spectra and DSC peak this two drugs combination may be chemically incompatible.
- Hence there arises a need to physically separate these two drugs this can be achieved by coating the granules of Benazepril and formulate the both drugs into a bilayer tablet.
- The bilayer tablet were prepared and optimized by  $3^2$  factorial designs. The optimized formulation was kept for stability study for 1 month at  $40^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$  & relative humidity  $75\% \pm 0.2\%$ .
- Thus it can be concluded that the bilayer tablet is the stable dosage form for the physically incompatible drugs Amlodipine Besylate and Benazepril hydrochloride.

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**Conflict of interest:**

The authors declare no conflict of interest.

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