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Research Article

DESIGN DEVELOPMENT AND EVALUATION OF BILAYER TABLETS CONTAINING PARACETAMOL AS SR LAYER AND N-ACETYL CYSTEINE AS IR LAYER

Premanjali Divya[1], Dr. Manish Kumar Gupta[2], Vijay Sharma[3]

[1] M.Pharm. Research Scholar, Department of Pharmaceutics, Jaipur College of Pharmacy, Jaipur, Rajasthan, India

[2] Professor and Principal, Jaipur College of Pharmacy, Jaipur, Rajasthan, India

[3] Associate Professor, Jaipur College of Pharmacy, Jaipur, Rajasthan, India

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ABSTRACT

Preformulation study for understanding the various physico-chemical properties of the N-Acetyl Cysteinelone and its interaction with various excipients. Weigh accurately 10 mg of N-Acetyl Cysteine and transfer to 100 ml volumetric flask. The drug was dissolved in small quantity of water and the volume was made upto 100 ml to obtain a stock solution of 100 µg/ml. 1 ml of this stock solution was again diluted with water upto 10 ml to obtain a stock solution of 10 µg/ml. The resulting solution was scanned between 200 nm to 400 nm in a double beam UV/ Visible spectrophotometer. The melting points of the drugs were determined by open capillary method. Accurately weighed samples of each drug (2 mg) were transferred to aluminium pans and sealed. All samples were run at a heating rate of 10^{o}C/min over a temperature range 40-43^{o}C using Shimadzu DSC-60 Thermal Analyzer. The Infra-red spectroscopy of the sample was carried out to ascertain identity of the drugs. A pellet of approximately 1 mm diameter of each drug was prepared by compressing 3-5 mg of the drug with 100-150 mg of potassium bromide in KBr press (Model M-15, Techno Search Instruments).pH of 1% solution of N-Acetyl Cysteine and Paracetamol were determined by digital pH meter. Solvents such as water, alcohol, methanol and isopropyl alcohol were used for the solubility studies. Hydroxypropyl methyl cellulose which is a hydrophilic polymer is chosen for retarding the drug release as it has got both swelling and matrix-forming properties. Disperse HPMC E5 in about 45% IPA under stirring for 10 min. After proper dispersion, add MDC and solubilize HPMC E5 and keep under stirring for 15 min. In any rational design and evaluation of dosage forms for drugs, the stability of the active component must be major criteria in determining their acceptance or rejection.

Keywords: N-Acetyl Cysteinelone,HPMC E5,bilayer tablets**,** SR layer, IR layer

INTRODUCTION:

A comprehensive preformulation study is essential for understanding the various physico-chemical properties of the N-Acetyl Cysteinelone and its interaction with various excipients. The choice of excipients is dictated by the type of dosage form to be developed. It forms the first step in the development of a robust dosage form that can sustain the rigors of processing and shelf life. Preformulation proves to be a cost-saving process in the long run, by reducing challenges during formulation development.

Preformulation studies include:

- Authentication of drug
- Evaluation of physico-chemical properties
- Evaluation of micromeritic properties
- Drug-excipient compatibility study

Authentication of drug:

a) UV spectrum of drug:

i) N-Acetyl Cysteine

Weigh accurately 10 mg of N-Acetyl Cysteine and transfer to 100 ml volumetric flask. The drug was dissolved in small quantity of water and the volume was made upto 100 ml to obtain a stock solution of 100 µg/ml. 1 ml of this stock solution was again diluted with water upto 10 ml to obtain

**Corresponding author: Premanjali Divya |*

a stock solution of 10 µg/ml. The resulting solution was scanned between 200 nm to 400 nm in a double beam UV/ Visible spectrophotometer (Shimadzu 1700).

ii) Paracetamol:

Weigh accurately 10 mg of Paracetamol and transfer to 100 ml volumetric flask. The drug was dissolved in water and the volume was made up to 100 ml to obtain a stock solution of 100 µg/ml. One ml of this stock solution was again diluted with water up to 10 ml to obtain a solution of 10 µg/ml. The resulting solution was scanned between 200 nm to 400 nm in a double beam UV/ Visible spectrophotometer (Shimadzu 1700).

b) Melting point:

The melting points of the drugs were determined by open capillary method. Drug was filled up to 4-5 mm in glass capillaries whose one end was sealed by flame. The drug containing capillary was dipped in liquid paraffin inside the melting point apparatus equipped with magnetic stirring facility for uniform heat transfer. Melting point temperature range was noted from when the drug just starts to melt till it completely melts. The experiment was done in triplicate and the average was noted.

c) Differential scanning calorimetric (DSC) studies

Accurately weighed samples of each drug (2 mg) were transferred to aluminium pans and sealed. All samples were run at a heating rate of 10^{o}C/min over a temperature range 40-43^{o}C using Shimadzu DSC-60 Thermal Analyzer.

d) Fourier transmission infrared (FTIR) spectroscopy of drug:

The Infra red spectroscopy of the sample was carried out to ascertain identity of the drugs. A pellet of approximately 1 mm diameter of each drug was prepared by compressing 3-5 mg of the drug with 100-150 mg of potassium bromide in KBr press (Model M-15, Techno Search Instruments). The pellet was mounted in IR compartment and IR spectrum of N-Acetyl Cysteine and Paracetamol were recorded at a resolution of 4cm-1 over a range of 4000-400 cm -1 using a Shimadzu Model 8400 FTIR. Nitrogen gas was purged at the rate of 50 ml/min to maintain inert atmosphere.

2. Evaluation of physico-chemical properties:

a) pH: pH of 1% solution of N-Acetyl Cysteine and Paracetamol were determined by digital pH meter.

b) Loss on drying (LOD): Sample was taken and 1 gm weighed and kept for checking the loss on drying on LOD apparatus Sartorius-MA45 at 105°C for 3 min. Percentage loss of moisture is determined.

MATERIALS & MRTHOD:

Table 1: Materials Used In Tablet Preparation

Sr. No.	Materials	Manufacture/ supplier
1.	N-Acetyl Cysteine (N-Acetyl Cysteine)	Hangzhou Verychem Science And Tech Co. Ltd
2.	Paracetamol (Paracetamol)	Farmson Analgesics
3.	Microcrystalline Cellulose	Accent Microcell Industries
4.	Dibasic Calcium Phosphate	SudeepPharma Ltd.
5.	Sodium Starch Glycolate	Maruti Fine Chemicals
6.	Colloidal Silicon Dioxide	Evonic Degussa Corp.
7.	Hydroxpropyl Methyl Cellulose	Dow Chemical Company
8.	Povidone	NanhanghIndusatrialCo.Ltd.
9.	Iso – Propyl Alcohol	S.D. Fine Chemicals,Mumbai
10.	Methylene Dichloride	S.D. FINE Methylene Dichloride
11.	Magnesium Stearate	S. Kant Healthcare Ltd.
12.	Titanium Dioxide	Kronos, Inc
13.	Talc	Vijay Minerals
14.	Quinoline Yellow Lake	Rockwood Pigments
15.	Vanills Flavour	Firmenich
16.	Menthol	Bhagat Aromatic Ltd.

2) List of equipments used: List of Equipments Used For Formulations:

Table 2: List of Equipments

Sr. No.	EQUIPMENTS	Manufacturer / Supplier
1.	Electronic Balance module-AUW 2200	Shimadzu Corporation, Japan.
2.	pH Meter	Metler Toledo, India.
3.	Electromagnetic Sieve Shaker	Elect Pharma
4.	Rapid Mixer Granulator	Sainath boilers, India
5.	Octagonal Blender	Gansons, India.
6.	Moisture Balance	Sartorius, Germany
7.	Vernier Calliper	Mitutoyo, Corps, Japan
8.	Vibratory Sifter	Gansons, India.
9.	Fluidized Bed Dryer	Alliance Engineering Co.
10.	Multi Mill	Gansons, India.
11.	Double rotary compression Machine	Eliza press, India.
12.	Stirrer	Remi motors
13.	Colloidal mill	Avon equipments
14.	Conventional coating Pan	GMI
15.	Strip packaging machine	GansonsPvt. Ltd.
16.	LOD Apparatus	Sartorius – MA 45
17.	Single rotary compression machine	Cadmach , India

3) List of instruments used for analysis List of Instrument used in tablet Analysis

Table 3: List of Instrument Used In Tablet Analysis

Sr. No.	Equipments	Manufacturer/supplier
1.	FT-IR Spectrophotometer 8300	Shimadzu-Corporation, Japan.
2.	HPLC with PDA/Binary System	Shimadzu-Corporation, Japan.
3.	UV Spectrophotometer	Shimadzu-Corporation, Japan
4.	Dissolution Apparatus TDT-08L	Electro lab, India.
5.	Friability Test Apparatus	Electro Lab, ET-2, India.
6.	Hardness Tester	Dr.SchleunigerPharmatron tester
7.	Tap Density Apparatus	Electrolab
8.	Friabilator	Electrolab
9.	Disintegration tester (USP)	Electro Lab, India
10.	DSC	Shimadzu-Corporation, Japan.

Hausner's Ratio	% Compressibility Index	Flow Description
1.00 – 1.11	≤ 10	Excellent
1.12—1.18	11-15	Good
1.19 – 1.24	16-20	Fair
1.25 -1.34	21 - 25	Possable
1.35 -1.45	26 -31	Poor
1.46 – 1.59	32 - 37	Very poor
>1.6	≥ 38	Very very poor

4. Drug-excipient compatibility study:

Excipients form a vital part of any formulation and it is necessary to ensure its suitability with the drug of choice. N-Acetyl Cysteine and excipients, when subjected together in a definite proportion and in determined conditions, show physical and chemical changes in case of incompatibility. There are different tests to evaluate this incompatibility. N-Acetyl Cysteine and Paracetamol with the excipients are taken in the following ratio and is kept in two different conditions (wet and dry) for the study.

Table 4: Compatibility (Drug A/B: Excipient) Ratio

Sr. No.	Composition	Ratio
1.	Drug	X
2.	Drug + Crospovidone	x:0.5
3.	Drug + Croscarmellose	x:0.5
4.	Drug + Sodium starch Glycolate	x:0.5
5.	Drug + PVP K30	x:0.5
6.	Drug + HPC-L	x:0.5
7.	Drug + HPMC E5	x:0.5
8.	Drug + MCC	x:1
9.	Drug + Lactose	x:1
10.	Drug + Mannitol	x:1
11.	Drug + Starch	x:1
12.	Drug + Aerosil	x :0.25
13.	Drug + Talc	x :0.25
14.	Drug + Magnesium Stearate	x :0.25
15.	Drug + Stearic acid	x :0.25
16.	Drug + HPMC K4 M	x : 0.5
17.	Drug + All excipients	x : 1
18.	Placebo	x : 1

Note:x = 1 if N – Acetyl Cysteine, x = 6.5 if ParacetamolStorage condition: The samples were kept at:-25 ± 3°C / 60 ± 5% RH**,** 40 ± 2 °C /75 ± 5% RH55°C

Observations:

Observations were made after 7, 15, 21 and 30 days. No changes were observed in samples kept at 25 ± 3°C / 60 ± 5% RH and 40 ± 2 °C /75 ± 5% RH.

At 55^0C change in appearance was observed with lactose, Croscarmellose sodium and Crospovidone and yellow lumps formed on 30 days.

Table 5: Compatibility [Drug (A + B): EXCIPIENTS] RATIO

Sr. No.	Composition	Ratio
1.	N – Acetyl Cysteine + Paracetamol	1 : 6.5
2.	N– Acetyl Cysteine + Paracetamol + Crosspovidone	1:6.5:0.5
3.	N- Acetyl Cysteine + Paracetamol + Croscarmellose	1:6.5:0.5
4.	N-AcetylCysteine+Paracetamol+SodiumstarcGlycolate	1:6.5:0.5
5.	N-Acetyl Cysteine+Paracetamol+PVP K 30	1:6.5:0.5
6.	N-Acetyl Cysteine+Paracetamol+HPC-L	1:6.5:0.5
7.	N-Acetyl Cysteine+Paracetamol+HPMC E5	1:6.5:0.5
8.	N-Acetyl Cysteine+Paracetamol+Mcc	1:6.5:1
9.	N-Acetyl Cysteine+Paracetamol+Lactose	1:6.5:1

10.	N-Acetyl Cysteine+Paracetamol+Mannitol	1:6.5:1
11.	N-Acetyl Cysteine+Paracetamol+Starch	1:6.5:1
12.	N-Acetyl Cysteine+Paracetamol+Aerosil	1:6.5:0.25
13.	N-Acetyl Cysteine+Paracetamol+Talc	1:6.5:0.25
14.	N-Acetyl Cysteine+Paracetamol+Magnesium Stearate	1:6.5:0.25
15.	N-Acetyl Cysteine+Paracetamol+Stearic acid	1:6.5:0.25
16.	N-Acetyl Cysteine+Paracetamol+HPMC K4 M	1:6.5:0.5

Combination of N-Acetyl Cysteine and Paracetamol with excipients for compatibility study: Observations:

❖ Observations were made after 7, 15, 21 and 30 days. No changes were observed in samples kept at 25 ± 3°C / 60 ± 5% RH and 40 ± 2 °C /75 ± 5% RH.

❖ At 55^0C change in appearance was observed with lactose, Croscarmellose sodium and Crospovidone and yellow lumps formed on 30 days.

1. Dose Calculation:

Any formulation developed is incomplete without deciding upon a proper dose. An optimum dosage regimen is the one in which the drug is administered in suitable doses, by suitable route, with sufficient frequency that ensures maintenance of plasma concentration within the therapeutic window without excessive fluctuation and N-Acetyl Cysteine accumulation for the entire duration of therapy. While calculating dose it was assumed that pharmacokinetic parameters of the drug would remain constant during the course of therapy and that the drug follows open compartment model. Based upon various market survey conducted on available marketed preparations of Paracetamol, it recommends a maximum of 1000 mg per dose (usually 2 tablets) and four such doses per day. So it is tentatively decided that a dose of 650mg/tab of Paracetamol is to be prepared with a sustained release. Its effectiveness can be determined only after assay and dissolution studies. Since N-Acetyl Cysteine is most commonly used for Paracetamol overdose, an attempt was made to formulate N-Acetyl Cysteine into a tablet form with a dose calculated on the basis of that used generally for treating overdose. So it was concluded to prepare a dose of 100mg/tab.

Binder: HPMC E5 in isopropyl alcohol (IPA) and methylene dichloride (MDC) **Glidant:** Aerosil 200**Lubricant:** Magnesium stearate **Disintegrant:** SSG A

Various excipients screened for preparation of sustained release layer of Paracetamol using wet granulation method included the following: **Binder:** PVP K30 in water **Lubricant:** Magnesium stearate

COMPOSITIONS: The compositions of various formulations which were prepared are as shown:

Table 6: Composition of trials

For Immediate release layer					
Ingredients	Quantity per tablet (mg)				
	F1	F2	F3	F4	F5
N-Acetyl Cysteine	100	100	100	100	100
MCC PH 101	82.1	71.3	63.4	54.7	50.7
SSG A	8.0	12.0	16.0	20.0	20.0
Vanilla flavour	-	2.0	3.5	4.4	4.4
Menthol	-	-	-	-	-
Aerosil 200	2.0	2.6	2.6	2.6	2.6
DCP Fine	55.0	55.0	55.0	55.0	55.0
Quinoline yellow lake	0.1	0.1	0.1	0.1	0.1
HPMC E5	5.0	6.0	7.0	7.8	7.8

IPA & MDC	Q.S	Q.S	Q.S	Q.S	Q.S
MCC PH 102	30.0	30.0	30.0	30.0	30.0
Aerosil 200	2.6	2.6	2.6	2.6	2.6
SSG A	3.0	5.0	7.0	10.0	10.0
Vanilla flavour	-	-	-	-	4.0
Menthol	-	-	-	-	
Quinoline yellow lake	0.2	0.2	0.2	0.2	0.2
Magnesium stearate	2.0	3.2	2.6	2.6	2.6
Total layer weight:	290.0	290.0	290.0	290.0	290.0

For Sustained release layer					
	Quantity per tablet (mg)				
Ingredients	F1	F2	F3	F4 (Optimised Batch)	F5 (Reproducible Batch)
Paracetamol	650	650	650	650	650
MCC PH 101	5.0	5.0	12.5	17.5	17.5
HPMC K100 LVCR	40.0	35.0	25.0	20.0	20.0
PVP K30	5.0	7.5	10.0	10.0	10.0
Purified water	-	-	-	-	-
MCC PH 102	35.0	35.0	35.0	35.0	35.0
Magnesium stearate	5.0	7.5	7.5	7.5	7.5
Total layer weight:	740.0	740.0	740.0	740.0	740.0
Tablet weight:	1030.0	1030.0	1030.0	1030.0	1030.0

For Immediate release layer					
Ingredients	Quantity per tablet (mg)				
	F6	F7	F8 (Optimised Batch)	F9 (Reproducible Batch)	F10 (Process Optimisation Batch)
N-Acetyl Cysteine	100	100	100	100	100
MCC PH 101	50.7	52.7	48.9	48.9	48.9
SSG A	20.0	20.0	20.0	20.0	20.0
Vanilla flavour	4.4	4.4	4.4	4.4	4.4
Menthol	-	2.0	3.0	3.0	3.0
Aerosil 200	2.6	2.6	2.6	2.6	2.6
DCP Fine	55.0	55.0	55.0	55.0	55.0
Quinoline yellow lake	0.1	0.1	0.1	0.1	0.1
HPMC E5	7.8	7.8	7.8	7.8	7.8
IPA & MDC	Q.S	Q.S	Q.S	Q.S	Q.S
MCC PH 102	30.0	30.0	30.0	30.0	30.0
Aerosil 200	2.6	2.6	2.6	2.6	2.6
SSG A	10.0	10.0	10.0	10.0	10.0
Vanilla flavour	4.0	-	-	-	-
Menthol	-	-	2.8	2.8	2.8

Quinoline yellow lake	0.2	0.2	0.2	0.2	0.2
Magnesium stearate	2.6	2.6	2.6	2.6	2.6
Total layer weight:	290.0	290.0	290.0	290.0	290.0

For Sustained release layer					
Ingredients	Quantity per tablet (mg)				
	F6	F7	F8	F9	F10(Process Optimisation Batch)
Paracetamol	650	650	650	650	650
MCC PH 101	17.5	17.5	17.5	17.5	17.5
HPMC K100 LVCR	20.0	20.0	20.0	20.0	20.0
PVP K30	10.0	10.0	10.0	10.0	10.0
Purified water	-	-	-	-	-
MCC PH 102	35.0	35.0	35.0	35.0	35.0
Magnesium stearate	7.5	7.5	7.5	7.5	7.5
Total layer weight:	740.0	740.0	740.0	740.0	740.0
Tablet weight:	1030.0	1030.0	1030.0	1030.0	1030.0

MANUFACTURING PROCEDURE:

A) For Immediate release layer:

1. Sifting: Sift N-Acetyl Cysteine, DCP, menthol and vanilla flavour through #40 ASTM.Co-sift Aerosil-200 and MCC PH 101 through #40 ASTM.Co-sift Quinoline yellow lake with SSG A through #100 ASTM.Co-sift all the above ingredients.

2. Dry Mixing: Transfer the sifted material to RMG and mix for 10 min with impeller at slow speed.

3. Granulation: HPMC E5 is dissolved in appropriate proportion of IPA and MDC to prepare binding solution.Run the impeller to granulate the dry mix with the binding solution till granules of required consistency is obtained.Run the chopper at slow speed if required.

4. Drying: Air dry the wet granules in fluidized bed dryer for 10 min and then dry the partially dried granules at an inlet temperature of 50˚C±5˚C until LOD of the granules reaches 1.5-2.5% w/w at 105˚C.

5. Milling and sifting: Sift the dried granules through #24 ASTM on vibrosifter. Mill the oversized dried granules in multimill using 2.0 mm screen using knifes forward at medium speed. Sift the milled granules through #24 ASTM.

C) For Coating: Coating of the tablets was done from batch no. F6 onwards.

Table 7: Coating formula

Ingredients	Quantity per tablet (mg)
HPMC E5	21.75
Talc	3.334
Titanium Dioxide	3.334
PEG 6000	3.334
Quinoline Yellow Lake	0.33
Vanilla flavor	0.67
Menthol	0.67
IPA	204
MDC	306
Weight gain:	20
Coated tablet weight:	1050

HPLC analysis of dissolution aliquots of N-Acetyl Cysteine and Paracetamol:

For standard preparation: Weigh 22 mg of N-Acetyl Cysteine in 200 ml volumetric flask. Add 70 ml dissolution medium to it and sonicate to dissolve. Then make up the volume with the dissolution medium.Weigh 72 mg Paracetamol in 100 ml volumetric flask. Add 30 ml dissolution medium to it and sonicate to dissolve. Then make up the volume with the dissolution medium.Further dilute 5 ml of solution A + 5 ml of solution B to 50 ml with diluents.

Test aliquots: After specified time intervals, aliquots of 10 ml were removed from dissolution vessels, filtered through 0.45µ filters. Further dilute 2 ml of filtrate to 20ml with dissolution medium. 20 µl of this solution was injected into HPLC column. The chromatograms were recorded and peak responses of N-Acetyl Cysteine and Paracetamol were measured.

STABILITY STUDIES

In any rational design and evaluation of dosage forms for drugs, the stability of the active component must be major criteria in determining their acceptance or rejection. During the stability studies the product is exposed to normal conditions of temperature and humidity. However, the studies will take a longer time and hence it would be convenient to carry out the accelerated stability studies where the product is stored under extreme conditions of temperature.

Tablets of batch F8 were subjected to stability studies.

A) Experimental:

Tablets of the optimized formulation (F8) were tested for stability under two conditions for a period of three months. All the tablets were packed in ALU-PVC- PVC-ALU type strip package. The tablets stored in stability chambers maintained at 40^0C/75% RH and 30^0C/65% RH, were evaluated for their physical characteristics, in vitro release and content of active ingredient at the end of 30 days, 60 days and 90 days of storage period.

RESULTS AND DISCUSSION:

1. **Authentication of drug:-**

a) UV spectrum of drug:

i) N-Acetyl Cysteine (N-Acetyl Cystine)

The solution of N-Acetyl Cysteine in water was found to have a λ max of 205nm. In the literature, λ max is reported as 205-210 nm. So the given sample complies with standard

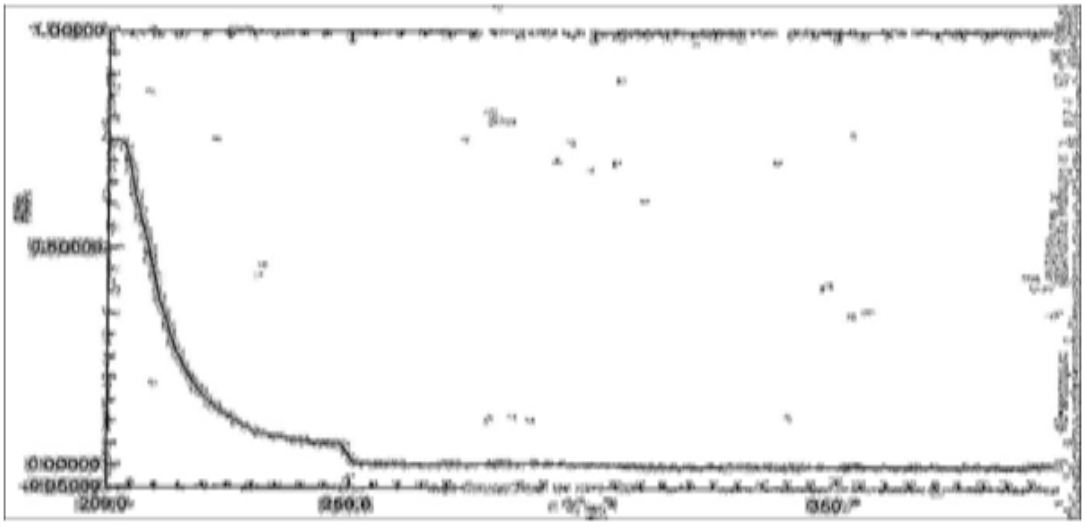

Fig 1: UV Spectrum for N-Acetyl Cysteine

ii) Paracetamol (Paracetamol)

The solution of Paracetamol in water was found to have a λ max of 245nm. In the literature, λ max is reported as 243 nm. So the given sample complies with standard.

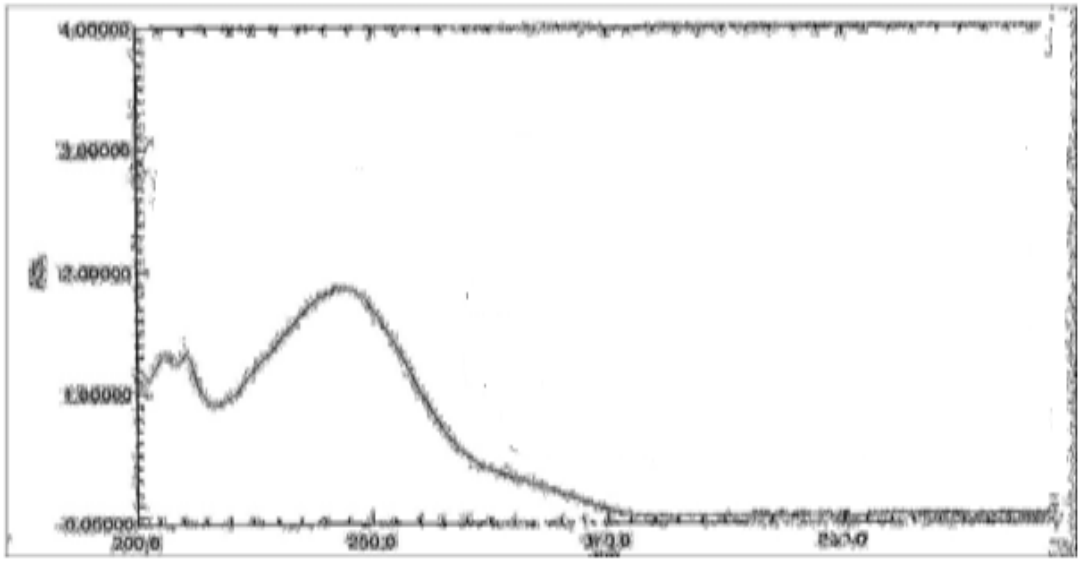

Fig 2: UV spectrum for Paracetamol

1) Pre-compression parameters: Results of all pre-compression parameters of all batches were tabulated as below:

For Blend of N-Acetyl Cysteine (Immediate release layer)

Table 8: Pre- compression Parameters for N-Acetyl Cysteine layer

Batch No.	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Compressibility Index (%)	Hausner Ratio	LOD (%)
F1	0.351	0.514	30.29	1.46	1.62
F2	0.384	0.538	28.62	1.40	1.87
F3	0.446	0.571	21.89	1.28	1.91
F4	0.518	0.625	17.12	1.20	1.73
F5	0.521	0.639	18.46	1.22	2.01
F6	0.530	0.648	18.20	1.22	2.34
F7	0.523	0.634	17.50	1.21	1.78
F8	0.512	0.629	18.60	1.22	1.99
F9	0.528	0.643	17.88	1.21	1.84
F10	0.519	0.636	18.39	1.22	2.11

Batches such as F1 and F2 Showed poor flow, Besides their low bulk densities,Compressibility Index and Hausner Ratio confirm the poor flow nature. Batch no. F3 showed just satisfactory flow. Batches F4-F10 showed considerably good flow and the proportion of granules:fines was also appropriate. Also, the bulk density values of these batches indicate that the powder has good packing character desirable for good compression. The LOD of all batches were also within the limits specified

In-vitro release profile for Paracetamol from Sustained Release layer:

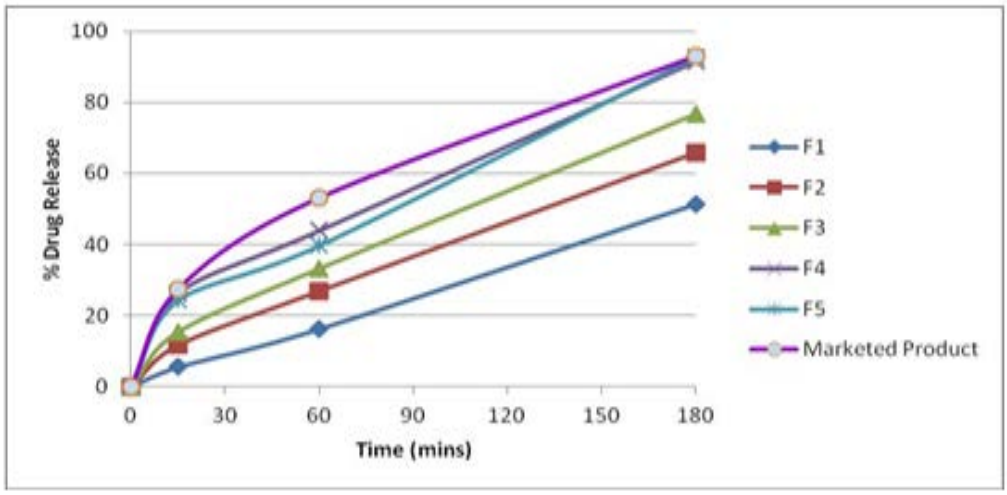

Fig 3: In-vitro drug release profile of batch nos. F1-F5

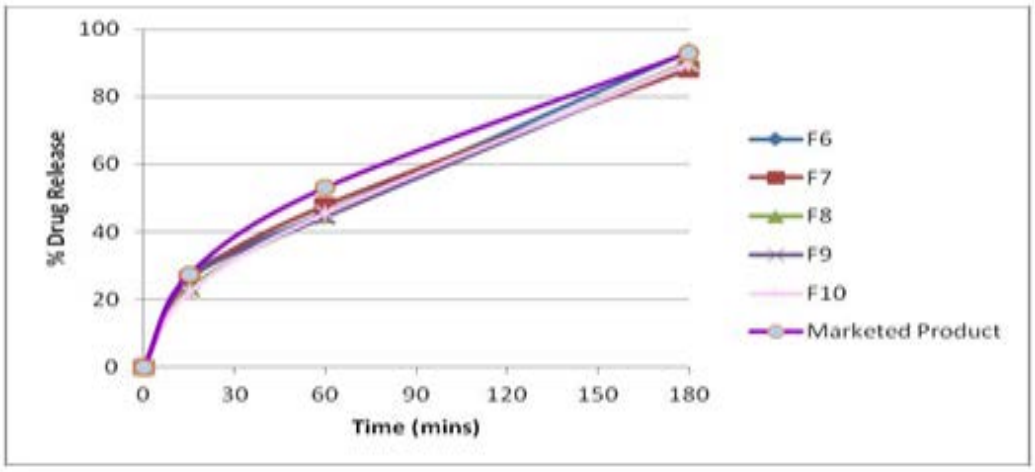

Fig 4: In-vitro drug release profile of batch nos. F6-F10

***In vitro* dissolution studies:**

a) At 30ºC/75% RH: The dissolution results obtained when the stability batch is kept under the condition (30ºC/65% RH) were as given in Table 1 and Table 2.

Table 9: Drug release of N-Acetyl Cysteine from IR layer of stability study samples at 30ºC/65% RH

Days	Immediate release layer			
	% Drug release			
	0 min	15 mins	60 mins	180 mins
0	0.0	39.37	79.64	100.05
30	0.0	40.11	81.73	99.20
60	0.0	42.34	83.71	99.76
90	0.0	43.20	80.46	98.97

CONCLUSION:

Thus the combination therapy of these two drugs increases the overall effectiveness and nullifies the side-effects of the therapy.

The main aim of the present work was to develop a bilayer drug delivery system which will sustain the release of paracetamol from the matrix whereas N-Acetyl Cysteine will release immediately after administration.

The compatibility of drugs with excipients was checked by DSC and FTIR studies. Calibration curve of N-Acetyl Cysteine and Paracetamol were constructed in dissolution medium[2 gm of NaCl + 7 ml of HCl in 1 L of water] pH 1.2 and mobile phase [Buffer: methanol(85:15 V/V); pH adjusted to 2.5 with OPA] using HPLC method.

Sustained release layer of Paracetamol was prepared using varying concentration of HPMC K100 LVCR and using PVP K30 in water as the binder. Immediate release layer of N-Acetyl Cysteine was prepared simultaneously using Sodium Starch Glycolate as super-disintegrant and HPMC E5 in IPA & MDC as binder.

The granules of both layers were evaluated for various physical parameters like bulk density, tapped density, Compressibility Index, Hausner Ratio and moisture content. Tablets were evaluated for various physical parameters such as thickness, hardness, friability, weight variation and assay. Formulations micrometrics, friability, assay, in vitro drug release in comparison with marketed product. The optimized batch (Batch F8) was subjected for short-term stability at 30^0C/65% RH and 40^0C/75% RH.

Major conclusions achieved from the investigation are as follows:

1. Structure of drugs and excipients was analyzed by FTIR and DSC which confirmed purity and authentication of drugs and excipients.
2. On the basis of the results of preformulation study, it was found that the presumed excipients can be used for formulation development. There was no incongruity between N-Acetyl Cysteine and excipients.
3. N-Acetyl Cysteine and Paracetamol showed poor flow properties, therefore wet granulation method was selected.
4. Based on dissolution study data of marketed formulation, specifications for drug release from developed formulation was decided.
5. After 3 months of accelerated stability studies, optimized formulation did not show any substantial change in physical characteristics, drug content and drug release. Thus the developed formulation was found to be stable.

The conclusion arrived in this thesis indicated that the bilayer tablet was found to have desired drug release pattern similar to that of marketed formulation. Thus the objectives envisaged in this thesis were fulfilled.

Further studies are needed to investigate the formulation for its performance in vivo and for establishment of in vitro and in vivo correlation.

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