FORMULATION DESIGN AND EVALUATION OF ORODISPERSIBLE TABLET OF ACETYLCYSTEINE USING SUPPERDISINTEGRANT.

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ABSTRACT

The aim of this work is to formulate and evaluate oral dispersing tablets of acetylcysteine to prevent disease associated with respiratory system mainly in bronchioles. Method which used for Preparation of tablet is direct compression method, with various super disintegrants like sodium starch glycolate, croscarmallose sodium, and Crospovidone at various concentrations (2%-20%). A total of eleven formulations were made using one type of super disintegrants for each formulation. Fourier Transmission InfraRed (FT-IR) and Differential Scanning Calorimetry studies (DSC) were performed to ensure the compatibility of drug with the super disintegrants. It was found to be satisfactory. The results of recompression studies reveals that the powder blends of all formulations acquire good flow properties. From the results of post compression studies for tablets of all formulations, it was concluded that the formulation containing 10% crospovidone as super disintegrants remerged as overall best formulation with lowest disintegration time and highest drug release rate.

Keywords: Acetylcysteine, Sodium starch stearate glycolate, Polymethacrylate, Microcrystalline cellulose, Lactose and Mannitol

1.INTRODUCTION

N-acetyl cysteine (NAC), as a safest and inexpensive medication. This drug is not available naturally, although cysteine is available in some meals like chicken, turkey meats, garlic, yogurt, and eggs. NAC is a well-tolerated mucolytic drug that moderates clinging mucous secretions and also enhances glutathione S-transferase activity. During oral administration, deacetylation reaction of NAC happens while passing along the small intestine as well as liver, thus its bioavailability is reduced to 4-10%. NAC stimulates and enhances glutathione biosynthesis, promotes detoxification, and acts directly as a scavenger of free radicals. It is a powerful antioxidant and a potential treatment option for diseases characterized by the generation of free oxygen radicals. NAC use in management and prevention of apoptosis and oxygen related genotoxicity in endothelial cells by enhancing intracellular levels of glutathione and decreasing mitochondrial membrane depolarization. The critical antioxidant power of NAC is due to its role as a precursor of glutathione, which is one of the most important naturally occurring antioxidants.

N-acetyl cysteine has critical anti-oxidant property along with it can also use in management, prevention and treatment of various disease like Chronic bronchitis Ulcerative colitis**,** Liver cancer**,** Muscle performance**,** Haemodialysis**,** Asthma**,** Alzheimer**,** Parkinson disease etc,

In the present study, we made an attempt to develop a stable and robust formulation of orodispersible tablet of acetylcysteine with optimum properties. To achieve this goal various formulation of acetylcysteine tablet were prepared and evaluated with respect to the various quality parameters both precompression parameter (bulk density, tapped density, compressibility index, hausne's ratio) and parameter for finished product (average weight, weight variation, tablet thickness, friability, hardness, disintegration time, drug content,) was optimized and evaluated.

2. Materials & Methods

Materials: Acetylcysteine was purchased from CHL laboratories, India and the other excipient like Sodium starch glycolate, Polymethacrylate, Microcrystalline cellulose, Lactose and Mannitol Magnesium stearate was obtained by Doshion Pharma-polymer Division, Ahmedabad, India.

Methods:

Procedure of orodispersible tablet of acetylcysteine

The composition of different formulations of acetyl cysteine orodispersible tablet is shown in table 1
Sod. CMC, mg. stearate and talc were weighed and pass through 40 # sieve. Weighed acetylcysteine and pass through 40 # sieve. Similarly, crospovidone and mannitol was passed through 40 # sieve. All the materials were blended in to the cage blender. Compression was done on 27-Station Machine (CMB3-D27 Cadmach, Ahmedabad, and India) using 8 mm FB with BL (Flat Bottom with Break Line) punch. (Procedure is same for all the formulation from F1 to F11)

***Table no :01 Optimized batch of orodispersible tablets**

Composition (mg)	**Batch code**										
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
Acetylcysteine	100	100	100	100	100	100	100	100	100	100	100
Microcrystalline cellulose	50	48	46	44	42	40	38	36	34	52	32
Mannitol	40	40	40	40	40	40	40	40	40	40	40
Mg. stearate	2	2	2	2	2	2	2	2	2	2	2
Talc	1	1	1	1	1	1	1	1	1	1	1
starch Sodium glycolate	2	2	2	2	2	2	2	2	2	2	2
Crospovidone	2	4	6	8	10	12	14	16	18	..	20
Polymethacrylate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Cherry flavour	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Total	200	200	200	200	200	200	200	200	200	200	200

Pre-compression parameter of formulated orodispersible tablet of acetylcysteine

Pre-compression parameter were determined in term of angle of repose, hausner's ratio, for determination of angle of repose (θ), the powder was poured through the walls of a funnel, which was fixed at a position such that its lower tip was at a height of exactly 2.0cm above hard surface. The powder was poured till the time when upper tip of the pile surface touched the lower tip of the funnel, calculate it using formula. Likewise calculate the hausner's ratio, car's index using their respective formulas.

Evaluation Of Orodispersible Tablet.

All the optimized orodispersible tablet of acetylcysteine were evaluated by using various official and un-official parameters such as friability, crushing strength, thickness, organoleptic characteristics, drug content etc.to determine best composition and formulation.

Disintegration Time

The superdisintegrant is an advantageous method in orodispersible tablet. Main salient feature of this Superdisintegrant Is They Increases Disintegrating Time Of Tablet And Improve Patient Compliances. The procedure of disintegration were performed as per mentioned in pharmacopeia. Three tablets from each formulated batch were evaluated for disintegration time by employing a modified dissolution apparatus Instead of the disintegration apparatus described in JP XII, a modified dissolution apparatus (JP XII paddle method) was employed. Water (900 ml), maintained at 37±0.5 0C was stirred with a paddle at 100 rpm. Disintegration time was measured when all the fragments of the disintegrated tablet passed through the screen of the basket.

Wetting Time and Water Absorption Ratio

The wetting time of the tablet was determined by placing five circular tissue papers (10 cm in diameter) in a Petri dish of 10 cm in diameter. Water (10 ml) containing methyl orange (0.1% w/v) was added to the Petri dish. A tablet was carefully placed on the surface of the tissue paper measured the time required for the dye to reach the upper surface of the tablet and recorded it as wetting time. The measurements were carried out in water. absorption ratio was calculated using Eq: Water absorption ratio = (Wa –Wb)/ Wb where Wb = weight of tablet before absorption of water, and Wa = weight of tablet after absorption of water.

In Vitro Drug Release

In vitro drug release studies were carried out using USP type II paddle type apparatus at 50 rpm. Phosphate buffer (900 ml) at pH 6.8 (corresponding to salivary pH) was used as the dissolution medium. The temperature of the dissolution medium maintained at 37 ±0.5 ^{o}c. An aliqout (5 ml) of dissolution medium was withdrawn at specific time intervals, filtered and suitably diluted before spectrophotometric analysis. Sink conditions were maintained by adding the medium with an equal amount (5 ml) of dissolution fluid. Absorption of the solution was measured by UV spectroscopy (Shimadzu-1700, Japan) at 210 nm. Dissolution rate was evaluated for all the formulations (F1-F11).

3 RESULT AND DISCUSSION

3.1 FT-IR Spectroscopy: FT-IR studies were carried out on order to determine purity of acetylcysteine and polymer use din preparation of orodispersible tablet and to determine the drug and excipient compatibility. Figure 1&2 shows the graphical representation of FT-IR spectroscopy of drug and excipients.

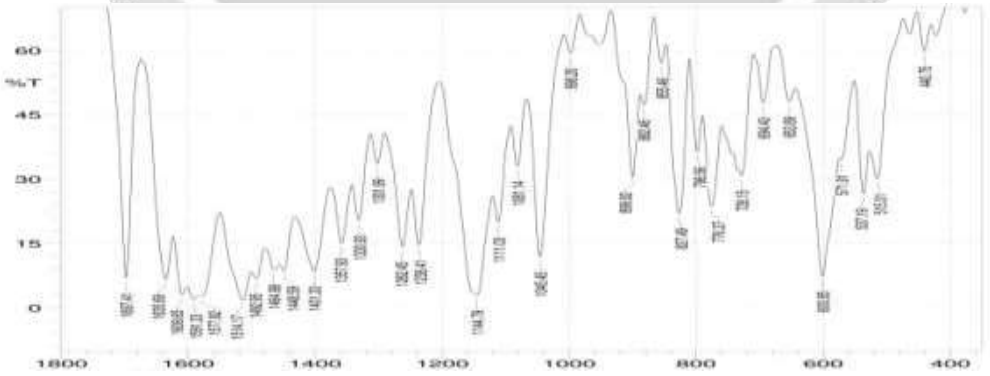

Figure No 01: FT-IR of pure drug (acetylcysteine)

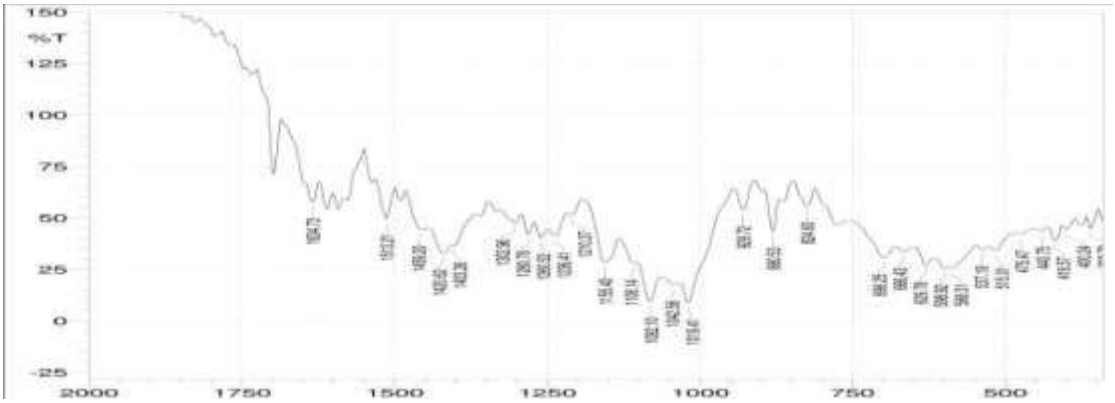

Figure No 02 : Infrared spectrum of acetylcysteine + excipient

3.2 Differential scanning calorimetry

DSC studies were carried out to identify purity of drug molecule Figure No 03 shows the graphical representation.

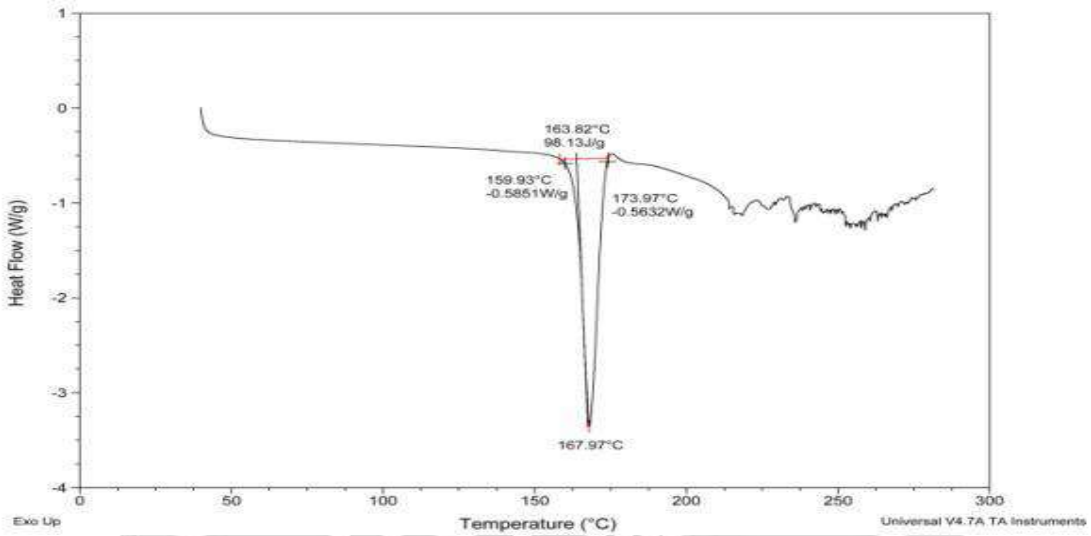

Figure No 03: DSC thermogram of acetylcysteine

3.3 Pre-compression parameter of formulated orodispersible tablet of acetylcysteine

The optimize formulation of orodispersible tablet were performed. Both official and unofficial test were pefromed for acetylcysteine tablet. The data obtain from this result is shown in below table.

Ingredients	Angle of Repose (θ)	Bulk Density (gm/cm^3)	Tapped Density (gm/cm^3)	Compressibility Index (%)	Hausner's Ratio (H_R)
F1	31.58	0.42	0.52	20.01	1.24
F2	32.39	0.46	0.58	21.52	1.27
F3	29.92	0.45	0.57	20.02	1.25
F4	30.39	0.45	0.49	07.13	1.07
F5	33.53	0.62	0.69	09.67	1.10
F6	29.93	0.60	0.66	09.42	1.10
F7	30.91	0.45	0.51	12.78	1.14
F8	30.44	0.49	0.57	13.37	1.15
F9	30.17	0.48	0.55	13.05	1.14

F10	28.03	0.41	0.48	13.32	1.15
F11	27.11	0.41	0.48	10.32	1.12

Table no 3.3 Pre-Compression Parameter

From above table the formulation no 11 shows excellent flow properties and F2 & F10 have good flow properties, all the result of precompression parameter were complied with pharmacopeial limit.

3.4 Post Compression Parameter Of Formulated Orodispersible Tablet Of Acetylcysteine:

The optimize formulation of orodispersible tablet were performed for both official and unofficial test for acetylcysteine tablet. The data obtain from this result is shown in below table. Thickness, friability, weight variation, hardness, drug content, disintegrating time, wetting time, water absorption ratio, this test were performed and found within pharmacopeial limit.

Ingredients	Thickness (mm)	Friability	Weight Variation (mg)	Hardness (kg/cm^2)
F1	2.52	0.52	200	2.12
F2	2.49	0.46	202	2.20
F3	2.48	0.84	202	1.98
F4	2.50	0.54	198	1.94
F5	2.52	0.65	194	2.24
F6	2.53	0.45	201	2.0
F7	2.54	0.84	198	2.10
F8	2.47	0.54	411	2.0
F9	2.49	0.39	402	2.13
F10	2.50	0.61	416	2.0
F11	2.50	0.48	410	2.0

Table No 3.4(a): post compression parameter of acetylcysteine

Ingredients	Drug content uniformity%	Disintegration time (min)	Water absorption ratio	Wetting time(sec)
F1	98.39	0.31	68.76	31
F2	99.19	0.34	50.09	22
F3	98.79	0.36	55.67	47
F4	98.59	0.28	60.38	39
F5	98.39	0.32	62.36	33
F6	98.19	0.30	58.86	29
F7	97.88	0.31	75.03	51
F8	97.58	0.25	77.95	68
F9	98.09	0.30	79.31	52
F10	97.99	0.27	50.45	53
F11	97.98	0.28	51.55	66

Table No 3.4(b): post compression parameter of acetylcysteine

From above data the hardness, thickness and diameters of all the tablets are uniform, which ensures that all the tablets were of uniform size and shape with good resistance against mechanical damage. F11 shows excellent result as compared to other formulations.

3.5 Wetting Ability (Wettability) Of Prepared Orodispersible Tablet;

From all the formulation only F-11 formulation shows best result from figure we can conclude that after 10 seconds the tablets wets completely. The data is shown in 3.4 (b).

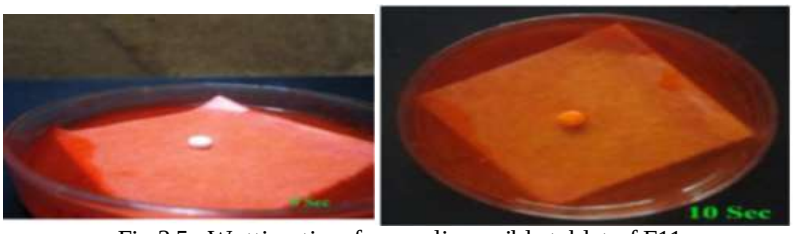

Fig.3.5: Wetting time for orodispersible tablet of F11

3.6 In-Vitro Dissolution Study

From the data The tablets of all the formulations were found to release more than 80% in 5 minutes, which is the desired quality of fast dissolving tablets that helps in faster absorption of the drug and quick onset of therapeutic effect. From all formulations F11 shows good dissolution properties. The data shown In table no:3.6

Time(sec)	% Drug release					
	F1	F2	F3	F4	F5	F6
1	0	0	0	0	0	0
2	16.40	23.30	22.55	20.47	20.96	22.40
3	31.60	40.60	50.65	32.87	32.15	40.60
4	56.70	51.40	75.75	55.05	55.57	70.30
5	70.80	76.60	92.22	77.82	78.60	85.02
6	80.75	94.69	99.78	85.68	88.70	92.36
7	95.35			91.35	98.95	
8				99.25		

Table No 3.6(a): In-Vitro dissolution study

Time(sec)	% Drug release				
	F7	F8	F9	F10	F11
0	0	0	0	0	0
1	21.50	32.40	30.52	25.35	52.63
2	42.60	53.59	55.60	49.80	72.63
3	63.35	75.82	72.20	80.60	99.60

Table No 3.6(b): In-Vitro dissolution study

The graphical representation of % drug release vs time is shown in above diagram from this we can conclude the best formulation.

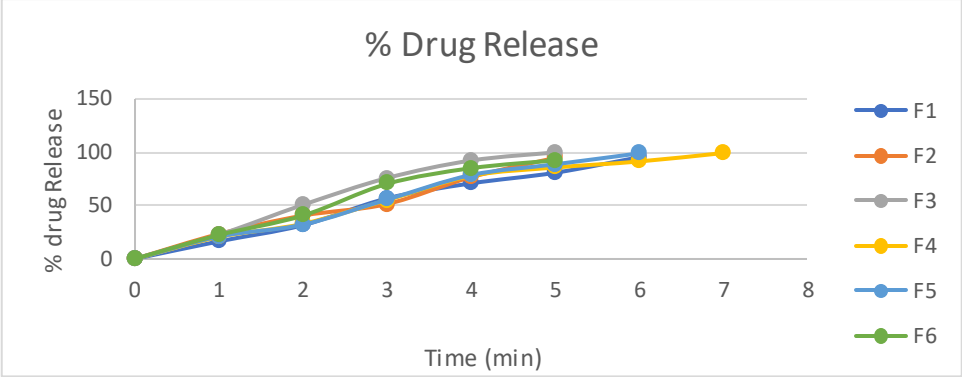

Figure no 3.6.1: Cumulative percent drug release of F1 – F6

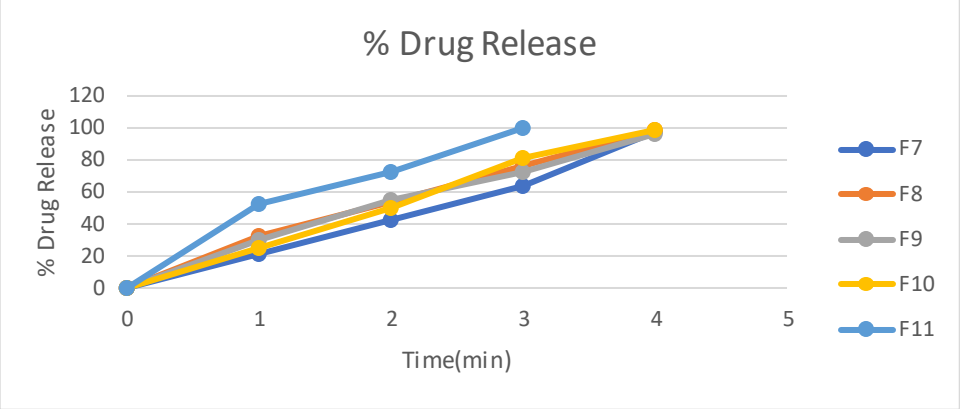

Figure no 3.6.2: Cumulative percent drug release of F7 – F11

From all the formulations F11 shows good pre-compression and post-compression parameters along with wettability (66 seconds) and in-vitro drug release 99.60 in 3 minutes.

CONCLUSION: It was concluded, that acetylcysteine can be successfully formulated as oral dispersible tablets using various super disintegrants in different concentrations by direct compression method. The formulation containing 20% of Crospovidone as super disintegrant was found to be outstanding than other formulations with good wettability and in-vitro dissolution properties.

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