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Der Pharmacia Sinica, 2011, 2 (3): 1-19

Der Pharmacia Sinica

ISSN: 0976-8688
CODEN (USA): PSHIBD

Modified release capsules of Ambroxil, Preformulation and evaluation

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ABSTRACT

The aim and objectives of the present study was to develop a pharmaceutically equivalent, stable, cost effective and quality improved formulation of Ambroxol pellets to present it in the form of capsules (Modified release capsules). To achieve this goal various prototype formulation trails were taken and evaluated with respect to the various quality control such as dissolution, assay, acid resistance and moisture content. The active pharmaceutical ingredient Ambroxol was subjected to preformulation study, and the results obtained with selected excipients showed good compatibility with Ambroxol. Ambroxol coated pellets were formulated by using commercially available pellets and Ambroxol coated pellets were filled by capsule filling machine. The stability of the capsules and pellet was determined by conducting "Accelerated stability testing" in 40°C ± 2°C / 75% ± 5%RH, 30ºC ± 2 ºC/ 65% ± 5% RH and 25±2°C/60±5% RH conditions for 1 month. Finally, af ter the duration, the product was analyzed for content and dissolution study. By the stability studies, the formulated Ambroxol modified release capsules and pellets proved to be stable throughout the period of the storage. The Ambroxol modified release pellets were loaded in size 4 capsules. It showed good results in formulation of stable dosage. Modified release pellets have minimum volume in size, greater surface area and more surface of disintegration time for pellets in capsules. Small volumes of pellets enter into the systemic circulation very fast. Moreover no accumulation of drug in the body occurs.

Key words: Modified release capsules, Ambroxil.

INTRODUCTION

Conventional drug products like tablets and capsules are formulated to release the active drug immediately to obtain rapid and complete systemic absorption of the drug. The conventional dosage form maintains the constant plasma drug concentration for the long period of time by administering in a particular dose and at particular frequency.

The terms sustained release, time release, prolong release or extended release are used to identify drug delivery systems that are designed to achieve a prolonged therapeutic blood or tissue

levels of the drug by continuous release for an extended period of time after administration of a single dose.

Extended release dosage forms release drug slowly ,so that plasma concentrations are maintained at a therapeutic level for a prolonged period of time (usually12 hrs). Extended drug action can be achieved at a predetermined rate by maintaining a relative constant drug level in the body with concomitant minimization of undesirable side effects that are associated with a saw tooth kinetic pattern of conventional release.[1-2]

The aim and objectives of the present study was to develop a pharmaceutically equivalent, stable, cost effective and quality improved formulation of Ambroxol pellets to present it in the form of capsules (Modified release capsules).

To achieve this goal various prototype formulation trails were taken and evaluated with respect to the various quality control such as dissolution, assay, acid resistance and moisture content.

Reasons For Developing Extended Release Drug Delivery System:
Immediate release of the active ingredient with resulting fast absorption rate may not always be desirable. If the drug has narrow therapeutic index, fast and complete absorption may result in plasma concentration that corresponds to toxic levels.

Rational Of Sustained Drug Delivery
Extended release tablets and capsules are commonly taken only once or twice daily. Typically extended release products provide an immediate release of drug which promptly produces the desired therapeutic effect which is followed by gradual and continual release of additional amounts of drug to maintain this effect over a predetermined period of time. The sustained plasma drug levels provided by extended release drug products often eliminate the need for night dosing, which provides benefit to the patient.

MATERIALS AND METHODS

Sugar spheres, HPMC E5,Aerosil,Ethyl Cellulose N50,PEG 6000,Talc USP, Isopropyl alcohol, Water, Ambroxol.

3. Preformulation studies

Preformulation activities range from supporting discovery's identification of new active agents to characterizing physical properties necessary for the design of dosage form. Critical information provided during preformulation can enhance the rapid and successful introduction of new therapeutics entities for humans. Preformulation testing is an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. It is the first step in the rational development of dosage form. [3]

3.1 Physical appearance:

White to yellowish crystalline powder

3.2 Solubility

The solubility of drug substance was performed in different solvents. The results are compiled in the below table 1.

Table1: Solubility

Solvent	Solubility
1)Water	Sparingly soluble
2)Methanol	Soluble
3)Methylene chloride	Practically insoluble .

3.3 Particle size distribution

Particle size of drug substance may affect the performance of the drug product in terms of dissolution and hence the bioavailability.

3.4 Determination of bulk density and tapped density

It refers to a measurement to describe packing of particles and also used to determine the amount of drug that occupies the volume in mg/ml before tapping and after tapping an accurately weighed quantity of the powder (W), was carefully poured into the graduated cylinder and the volume (V_o) was measured, then the graduated cylinder was closed with lid, set into the density determination apparatus. The density apparatus was set for 500 taps and after that, the volume (V_f) was measured and continued operation till the two consecutive readings were equal. The bulk density and tapped density were calculated using the following formula:

$$\textbf{Bulk density} = W / V_o$$

$$\textbf{Tapped density} = W / V_f$$

Where,

W = weight of the powder

V_O = intial volume

V_F = final volume

3.5 Compressibility index

Compressibility index is indirectly related to the relative flow rate, cohesiveness and particle size of a powder. The compressibility of a material can be estimated from the tap and bulk density measurements. The compressibility index of Ambroxol is calculated and given below. Compressibility was calculated from the powder density using the following formula:

$$\% \text{ Compressibility} = \frac{(P_t - P_O)}{P_t} \times 100$$

Where, P_t= Tapped density and P_O = Bulk density

3.6 Hausner's ratio

Tapped density and bulk density were measured and the Hausner's ratio was calculated using the formula,

$$\text{Hausners ratio} = \rho t/\rho o$$

Where, ρ_t = Tapped density

ρ_o = Bulk density

3.7 Melting point

It was determined by Mel-Temp melting point apparatus.

Sieve analysis

A series of standard sieve were stacked one above the other so that sieves with larger pore size (less sieve number) occupy top position followed by sieves with smaller pore size (greater sieve number towards the bottom)

Table 2: Seive Analysis

Sieve no	Empty sieve(gm)
#20	321.4
#30	328.6
#40	299.0
#60	287.2
#100	255.0
#120	274.0
#200	270.0
Receiver	348.8

Procedure

A series of sieves were arranged in the order of their decreasing pore diameter (increasing sieve number) i.e. sieve number 20, 30, 40, 60, 100, and 200. 100 grams of drug was weighed accurately and transferred to sieve number 20 which were kept on top. The sieves were shaken for about 5-10 minutes. Then the drug retained on each sieves was taken, weighed separately and amount retained was expressed in terms of percentage.

Table 3: Sieve Analysis

Sieve no	Empty sieve (gm)	Sample sieve (gm)	Difference (gm)	% Retained	% Cumulative retained
#20	321.4	321.4	0	0	0
#30	328.6	328.8	0.2	0.2	0.2
#40	299.0	300.0	1.0	1.0	1.2
#60	287.2	297.4	10.2	10.2	11.4
#100	255.0	275.0	20.0	20.0	31.4
#120	274.0	299.0	25.0	25.0	56.4
#200	270.0	303.2	33.2	33.2	89.6
Receiver	348.8	359.0	10.2	10.2	99.8

Weight of sample=100gm

Through this sieve analysis we came to know that as large quantity of powder was retained on sieve no. 200, which indicates poor flow of the drug. Flow property and particle size are inversely proportional to each other as Ambroxol has fine grade of particles, it has good flow.

3.8 Excipient Compatibility Studies

Compatibility studies were carried out to study the possible interactions between Ambroxol and other inactive ingredients in the formula.

3.8.1 Accelerated Compatibility Studies:

The physical compatibility of Ambroxol drug substance with various excipients was carried out with an aim to select suitable excipients for a stable and robust formulation. A blend of the drug with the excipients in suitable ratios (1:5) was filled in double lined poly bag (for exposing to 40°C/ 75%RH) and filled in glass vials to keep at 60°C. They were observed for any physical change against control samples kept at refrigerated condition (4°C).

Procedure

The compatibility studies were carried out at 40^{o}C/75% RH for 1, 2, 3 & 6 months and control samples were to be kept at 2-8^{o}C. With respect to physical and chemical aspects, they were tested.

3.9 Calibration curve of Ambroxol:

Table 4: Calibration Curve of Ambroxol

S. No.	Concentration (µg/ml)	Absorbance (nm)
0	0	0
1	5	0.2316
2	10	0.4016
3	15	0.5730
4	20	0.7665
5	25	0.9508

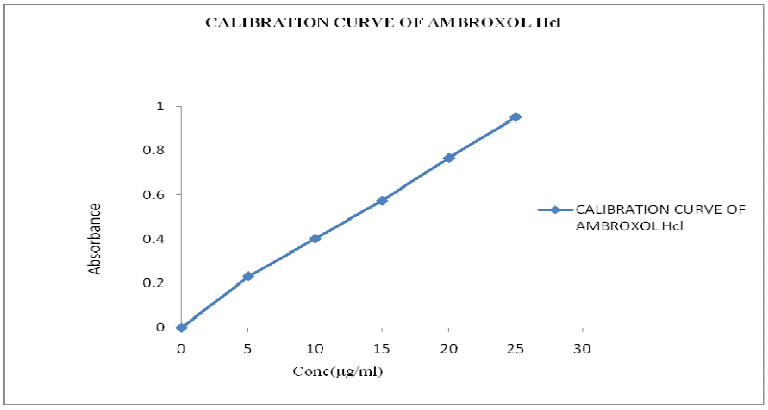


Figure 1: Calibration Curve Of Ambroxol

4. Stability Study :

For all the pharmaceutical dosage forms it is important to determine the stability of the dosage form. This includes storage at both normal and exaggerated temperature conditions, with the necessary extrapolations to ensure the product will, over its designed shelf life, provide medication for absorption at the same rate as when originally formulated. The design of the formal stability studies for the drug product should be based on the knowledge of the behaviour and properties of the drug substance and formal stability studies on the drug substance.

Storage Conditions
In general, a drug product should be evaluated under storage condition that tests its stability and if applicable, its sensitivity to moisture or potential for solvent loss. The long term testing should cover a minimum of 12 months study or at least three batches at the time of submission and should be continued for a period of sufficient time till it covers the proposed shelf life. Accelerated, intermediate storage conditions for drug products are given below.

Storage Conditions in Stability Study :
Stability samples are stored at
Accelerated Stability: 40±2°C/75±5% RH.
Intermediate Stability: 30±2°C/65±5% RH.
Long term Stability: 25±2°C/60±5% RH.

Testing Intervals for
Accelerated Stability: Initial, 1, 2, 3 & 6 months.
Long term Stability: Initial, 3, 6, 9, 12, 18, 24 & 36 months.
Intermediate Stability: Initial, 3, 6, 9 & 12 months.

When significant change occurs at any time during 6 months testing at the accelerated storage condition, additional testing at the intermediate storage condition should be conducted and evaluated against significant change criteria.

In general significant change for a drug product is defined as, a 5% change in assay from its initial value or failure to meet the acceptance criteria for when using biological or immunological procedures.

Experimental Section
Formulation Development
Drug loading & blending:
Ambroxol Hcl and Aerosol are blended in a blender for 30 minutes.

Pulverization:
Pulverize the blended Ambroxol Hcl with excipients separately through pulverizer fitted with 0.5mm screen and collect the material.

Binder solution preparation:
Sugar and HPMC E5 were mixed in a container containing purified water under continuous stirring till a clear solution obtained. The above solution is filtered through (#200) Nylon cloth.

Pellatization:
Sugar spheres were loaded into coating pan and the coating pan was allowed to rotate. The compressed air pressure was maintained at 1.0-2.0 kg/ cm ^{2}. Start the peristaltic pump and adjust to 10-40 RPM. Start spraying the sugar syrup solution adjusting the gun distance (30-40 cm). Continue spraying until the beads become wet. Stop spraying and add drug mixture in small quantities to the wet beads in the coating pan until the beads are free flowing. Disperse the talc in to remaining half quantity of purified water. Now add the solution obtained in above step into the

solution of enteric coating with continuous stirring. Finally pass the above solution of through (#200) Nylon cloth and collect the solution separately.

Coating:
Load the Drug Loaded pellets into FBC(Fluid Bed) bowl. Set the inlet temperature to 45°-55°C, bed temperature 40°-45°C. Coat the Drug Loaded pellets by bottom spray wurster at peristaltic pump rpm of 15 -100 and atomizing air pressure of 3.0 – 5.0 Kg/cm^2 with enteric coating solution till the coating solution is completed. Dry the pellets in FBC for about 30 min before unloading.

Sifting:
Sift the dried pellets through # 16 and collect # 16 retains and passings separately. Now pass # 16 passing pellets through # 20 and Collect retains and passings separately.

Packaging and storage:
Collect sifted Ambroxol Hcl pellets (#16 - #20) in HDPE containers lined with virgin double polythene bags. Transfer the HDPE container in to Finished Goods Store and store below 25 º C

Filling:
Fill the pellets into capsules.

Evaluation Of Capsules:
Weight variation test
Individual weights of 20 capsules were taken and the average weight was calculated by using the following formula.

$$\text{Weight variation} = \frac{\text{(Weight of capsule-Average weight)}}{\text{Average weight of capsules}} \times 100$$

DISSOLUTION

Preparation of P^H 6.8 Phosphate buffer
Dissolve 6.8g of Potassium dihydrogen orthophosphate in 1000ml of water and mix well. Adjust the pH of the solution to 6.8 with sodium Hydroxide or Hydrochloric acid.

Dissolution Parameters

Apparatus	USP Type-I (Basket)
Volume	900 ml
RPM	50
Medium	pH 6.8 phosphate Buffer
Drug release time	1^{st} hour,4^{th} hour,8^{th} hour
Temperature	37± 0.5º C

Standard solution:
Transfer about 25 mg of Ambroxol Hydrochloride working standard, accurately weighed, to a 50 ml volumetric flask add 20 ml of methanol, sonication for 15 minutes and dilute with methanol

to volume mix and filter. Transfer 1 ml of this solution to a 50 ml volumetric flask, dilute with dissolution medium to the volume and mix.

Sample preparation:
Set the parameters of dissolution apparatus as mentioned above. Place the pellets equivalent to 120 mg of Ambroxol Hydrochloride into each of six dissolution jars. At the end of specified time interval (1^{st} hour, 4^{th} hour,8^{th} hour) withdrawn 10 ml of the sample solution from each dissolution jar and replace with the same volume of dissolution medium previously maintained at 37 ± 0.5 ºC. And filter the solution through 0.45 µ nylon filter paper. Transfer 2 ml of above solution to a 25 ml volumetric flask and make up to the mark with dissolution medium.

Procedure:
Concomitantly determine the absorbance's of standard and sample solution of Ambroxol Hydrochloride in 1 cm cells at wavelength of maximum absorbance at about 244 nm with a suitable spectrophotometer, using dissolution medium as blank.

Table 4: Specification for dissolution profile

Tolerances(Hrs)	Specification
1^{st} Hour	Not more than 35% of Label Claim
4^{th} Hour	Not more than 70% of Label Claim
8^{th} Hour	Not less than 75% of Label Claim

Assay (By UV)
Preparation of standard solution
Weigh accurately about 50mg of Ambroxol Hydrochloride working standard, transfer to a 100ml volumetric flask add 60ml of Methanol, sonicate for 10 minutes to dissolve the content and make up to mark with methanol. Mix and filter through 0.45 µ nylon filter paper. Transfer 2 ml of above solution to a 100 ml volumetric flask and make up to the mark with dissolution medium.

Preparation of sample solution
Transfer an accurately weighed quantity of the powdered pellets equivalent to about 50 mg Ambroxol Hydrochloride volumetric flask, ad 60ml 0f methanol, sonicate for 15 minutes and cool the solution to room temperature and dilute with methanol to volume. Mix and filter the solution through 0.45µ nylon filter paper. Transfer 2 ml of above solution to a 100 ml volumetric flask and make up to the mark with dissolution medium.

Procedure:
Concomitantly determine the absorbance's of standard and sample solution of Ambroxol Hydrochloride in 1 cm cells at wavelength of maximum absorbance at about 244 nm with a suitable spectrophotometer, using dissolution medium as blank.

Disintegration:
The compendial disintegration test for hard and soft capsules follows the same procedure and uses the same apparatus as is for uncoated tablets. The capsules are placed in the basket rack assembly, which is repeatedly immersed 30 times per minute into a thermostatically controlled

fluid at 37ºc and observed over the time described in the individual monograph. To fully satisfy the test the capsules disintegrate completely into a soft mass having no palpably firm core, and only some fragments of the gelatin shell.

RESULTS AND DISSCUSION

The present study was undertaken to formulate Ambroxol modified release pellets and pellets presented in the capsules. The study involves preformulation studies of drug and excipients, formulation and processing development along with evaluation of capsules and pellets made with the optimized formulation. Finally modified release capsules were evaluated by *invitro* methods.

Table 5: Preformulation Studies

S. No.	Characteristics	Results
1.	Physical appearance	Yellowish crystalline powder.
2.	Solubility	Sparingly soluble in water, Sparingly soluble in Methanol, and Practically insoluble in Methylene chloride.
3.	Bulk density	0.913 gm/ml
4.	Tap density	0.934 gm/ml
5.	Compressibility index	2.24%
6.	Hausner's ratio	1.02%
7.	Melting point	238 ^{0}C
8.	Molecular weight	414.57

Table 6: Sieve Analysis

Sieve no	Empty sieve (gm)	Sample sieve (gm)	Difference (gm)	% Retained	% Cumulative retained
#20	321.4	321.4	0	0	0
#30	328.6	328.8	0.2	0.2	0.2
#40	299.0	300.0	1.0	1.0	1.2
#60	287.2	297.4	10.2	10.2	11.4
#100	255.0	275.0	20.0	20.0	31.4
#120	274.0	299.0	25.0	25.0	56.4
#200	270.0	303.2	33.2	33.2	89.6
Receiver	348.8	359.0	10.2	10.2	99.8

Table 7 : Accelerated Compatibility Studies

S. No	Composition Details	Observations		
		Storage Condition / Duration		
		Initial	40°C/ 75%RH	60°C
			1M	
1.	Ambroxol	A White crystalline powder	NCC	
2.	Ambroxol and Sugar spheres (20-24mesh)	A White color Powder	NCC	
3.	Ambroxol and Ethyl Cellulose N50	A White color Powder	NCC	
4.	Ambroxol and Povidone	A White color Powder	NCC	
5.	Ambroxol and PEG	A White color Powder	NCC	
6.	Ambroxol and Talc	A White color powder	NCC	
7	Ambroxol and Aerosil	A White color powder	NCC	
8	Ambroxol and HPMC E5	A White color powder	NCC	

*NCC : No Characteristic Change, *There was no interaction between drug and excipients. So the selected excipients were found to be compatible with Ambroxol .*

Weight of sample=100gm
Through this sieve analysis we came to know that as large quantity of powder was retained on sieve no. 200, which indicates poor flow of the drug. Flow property and particle size are inversely proportional to each other as Ambroxol has fine grade of particles, it has poor flow.

Compatibility Studies

The observations are recorded below.

Formulation Studies

Formulation studies Ambroxol hydrochloride Modified release capsules is based on preformulation data of various excipients selected and their compilation was shown in the following Table 8.

Table 8: Formulas and their quantities as per percentage w/w

S. No	INGREDIENTS	F1	F2	F3	F4	F5	F6	F7
1	Sugar Spheres (#20-#24)	54.22	54.22	54.22	54.22	54.22	54.22	54.22
2	Ambroxol Hcl	37.00	37.00	37.00	37.00	37.00	37.00	37.00
3	Aerosil	1.25	1.25	1.25	1.25	1.25	1.25	1.25
4	Sugar	03.50	03.50	03.50	03.50	03.50	03.50	03.50
5	HPMC E5	00.70	00.70	00.70	00.70	00.70	00.70	00.70
6	Purified Water(ml)	10.00	10.00	10.00	10.00	10.00	10.00	10.00
7	Ethyl Cellulose N50	1	1.6	02.10	1.2	0.6	0.8	1.1
8	PVP K30	0.3	0.4	00.32	0.32	0.24	0.32	0.32
9	PEG 6000	0.13	0.142	00.63	0.152	0.084	0.112	0.142
10	Talc	0.18	0.2	00.28	0.28	0.15	0.2	00.2
11	Isopropyl Alcohol	390 ml	290 ml	360 ml	350 ml	157 ml	210 ml	290 ml
12	Purified Water	20 ml	15 ml	20 ml	15 ml	7 ml	10 ml	15 ml

Formulation Development: Trial-1(F1)

Table 9: Composition of Trial 1

S.No	INGREDIENTS	F1
1	Sugar Spheres (#20-#24)	54.22
2	Ambroxol Hcl	37.00
3	Aerosil	1.25
4	Sugar	03.50
5	HPMC E5	00.70
6	Purified Water	10.00 ml
7	Ethyl Cellulose N50	1
8	PVP K30	0.3
9	PEG 6000	0.13
10	Talc	0.18
11	Isopropyl Alcohol	390 ml
12	Purified Water	20 ml

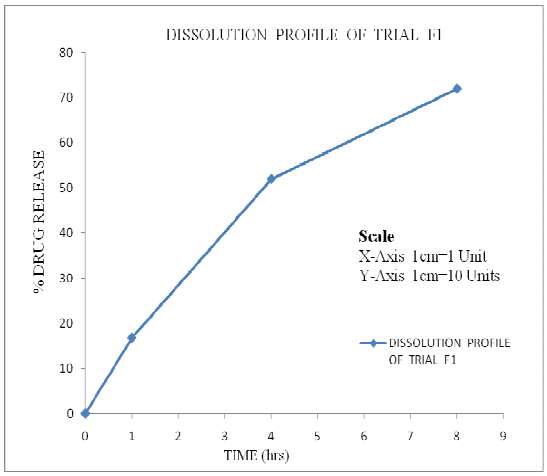


Figure 2: Dissolution Profile Of Trial 1(F1)

**Drug release at 8th hour did not match the specification.*

Formulation Development: Trial-2(F2)

Table 10: Composition of Trial 2

S.No	INGREDIENTS	F2
1	Sugar Spheres (#20-#24)	54.22
2	Ambroxol Hcl	37.00
3	Aerosil	1.25
4	Sugar	03.50
5	HPMC E5	00.70
6	Purified Water	10.00 ml
7	Ethyl Cellulose N50	1.6
8	PVP K30	0.24
9	PEG 6000	0.142
10	Talc	0.2
11	Isopropyl Alcohol	290 ml
12	Purified Water	15 ml

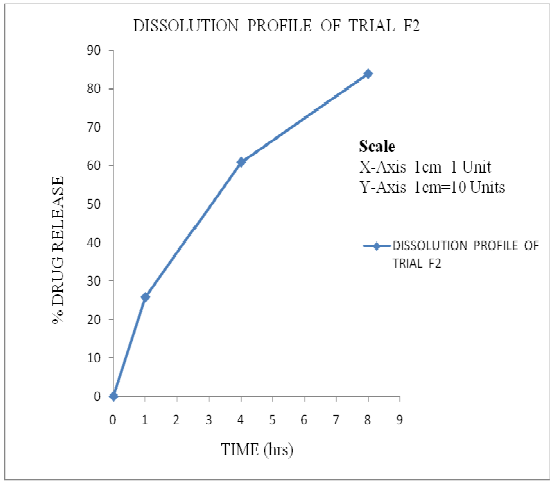


Figure 3 : Dissolution Profile Of Trial 2(F2)

**The concentration of ECN 50 and PVP- K 30 were altered i.e., increased to modify the release. In spite of this attempt made, release of drug at 8th hour exceeded the specification.*

Formulation Development: Trial-3(F3)

Table 11: Composition of Trial 3

S.No	INGREDIENTS	F3
1	Sugar Spheres (#20-#24)	54.22
2	Ambroxol Hcl	37.00
3	Aerosil	1.25
4	Sugar	03.50
5	HPMC E5	00.70
6	Purified Water	10.00 ml
7	Ethyl Cellulose N50	02.10
8	PVP K30	00.32
9	PEG 6000	00.63
10	Talc	00.28
11	Isopropyl Alcohol	360 ml
12	Purified Water	20 ml

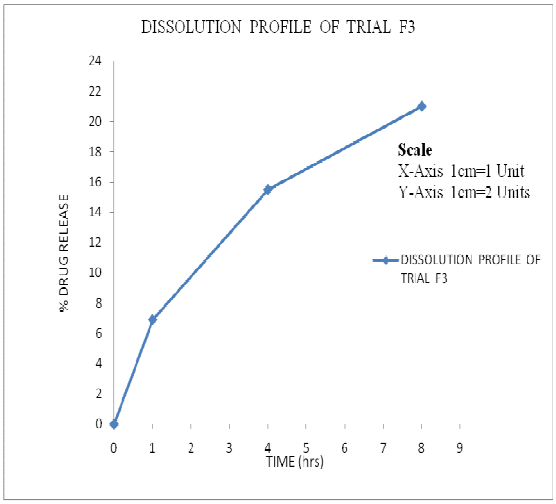


Figure 4: Dissolution Profile Of Trial 3(F3)

**The concentration of ECN 50 was increased and PVP- K 30 was decreased. Drug release was very poor when compared.*

Formulation Development: Trial-4(F4)

Table 12: Composition of Trial 4

S.No	INGREDIENTS	F4
1	Sugar Spheres (#20-#24)	54.22
2	Ambroxol Hcl	37.00
3	Aerosil	1.25
4	Sugar	03.50
5	HPMC E5	00.70
6	Purified Water	10.00 ml
7	Ethyl Cellulose N50	1.2
8	PVP K30	0.32
9	PEG 6000	0.152
10	Talc	0.28
11	Isopropyl Alcohol	350 ml
12	Purified Water	15 ml

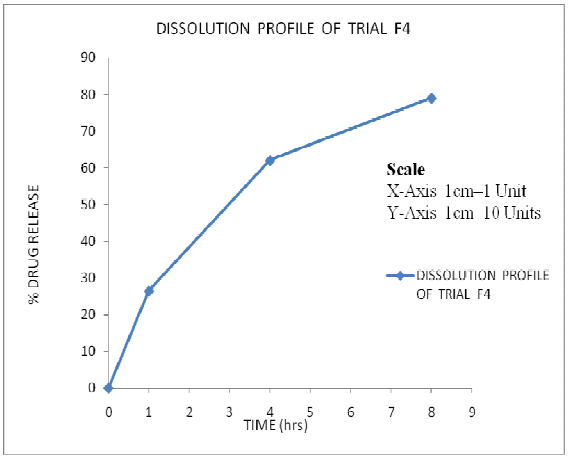


Figure 5: Dissolution Profile Of Trial 4(F4)

**In this formulation, the concentration of ECN 50 was decreased. Drug release at 8th hour proved to have exceeded the limit.*

Formulation Development: Trial-5(F5)

Table 13: Composition of Trial 5

S.No	INGREDIENTS	F5
1	Sugar Spheres (#20-#24)	54.22
2	Ambroxol Hcl	37.00
3	Aerosil	1.25
4	Sugar	03.50
5	HPMC E5	00.70
6	Purified Water	10.00 ml
7	Ethyl Cellulose N50	0.6
8	PVP K30	0.24
9	PEG 6000	0.084
10	Talc	0.15
11	Isopropyl Alcohol	157 ml
12	Purified Water	7 ml

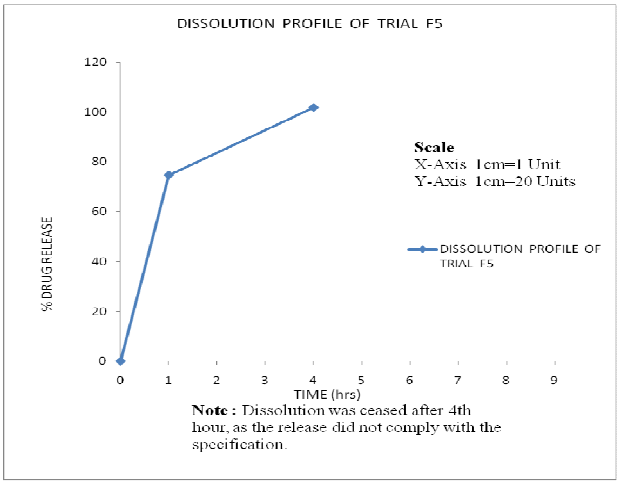


Figure 6: Dissolution Profile Of Trial 5(F5)

**The concentrations of both of ECN 50 and PVP K30 were decreased. This trial had over release of the drug at 1st and 4th hour. So, this hinted the cease of further dissolution.*

Formulation Development: Trial-6(F6)

Table 14: Composition of Trial 6

S.No	INGREDIENTS	F6
1	Sugar Spheres (#20-#24)	54.22
2	Ambroxol Hcl	37.00
3	Aerosil	1.25
4	Sugar	03.50
5	HPMC E5	00.70
6	Purified Water	10.00 ml
7	Ethyl Cellulose N50	0.8
8	PVP K30	0.32
9	PEG 6000	0.112
10	Talc	0.2
11	Isopropyl Alcohol	210 ml
12	Purified Water	10 ml

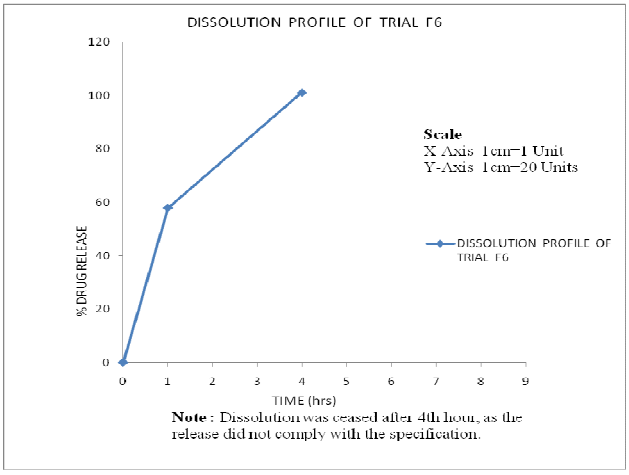


Figure 7: Dissolution Profile Of Trial 6(F6)

**In this trial, the concentrations of both of ECN 50 and PVP K30 were increased.Drug release at 1st hour and 4th hour did not comply with the standards.This trial was proved to be unsuccessful.*

Formulation Development: Trial-7(F7)

Table 15: Composition of Trial 7

S.No	INGREDIENTS	F7
1	Sugar Spheres (#20-#24)	54.22
2	Ambroxol Hcl	37.00
3	Aerosil	1.25
4	Sugar	03.50
5	HPMC E5	00.70
6	Purified Water	10.00 ml
7	Ethyl Cellulose N50	1.1
8	PVP K30	0.32
9	PEG 6000	0.142
10	Talc	00.2
11	Isopropyl Alcohol	290 ml
12	Purified Water	15 ml

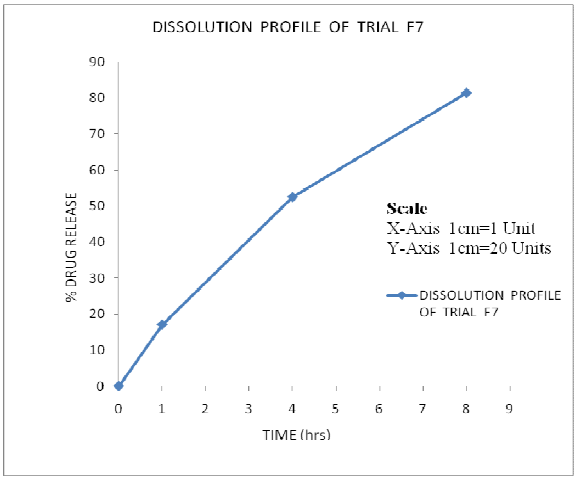
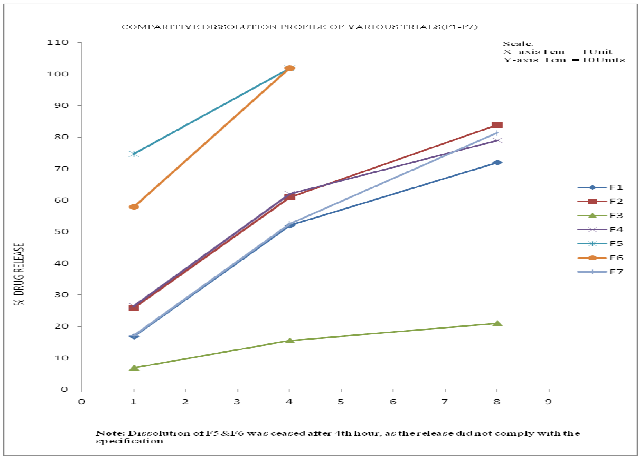


Figure 8: Dissolution Profile Of Trial 7(F7)

**This trail proved to be successful as the release profile perfectly matched the specification when the concentration of EC N50 was increased.*

Figure 9: Comparative Dissolution Profile of various Trials(F1-F7)



Loading of coated pellets into capsules

The pellets after checking physical parameters this can be filled into capsules No.2 by using automatic capsule filling machine and the weight of capsule can be checked in filling of pellets into capsules. The percentage weight variation of capsules is given as 5% to the total fill weight of capsule No.2 with sugar dummy pellets of same (#120-24 #) size.

Characteristics of pellets for trial F7

Characteristics of pellets of optimized batch F7

Core pellets	Results
Yield (Limit-NLT 97%)	99.6%
Bulk density	0.913 gm/ml
Tapped density	0.934 gm/ml
Compressibility index	2.24%
Hausner's ratio	1.02
Sieve analysis for 100 gm for uncoated	
# 16 passed	99 g
# 20 retained	99 g
#16 passed and 20 retained	99 g
Coated pellets	
Yield (Limit-NLT 96%)	99%
Sieve analysis for 100 gm	
#16 passed	98 g
#20 retained	98 g
# 16 passed and 20 retained	98 g
Bulk density	0.938 g/ml
Tapped density	0.962 g/ml
Compressibility index	2.49
Hausner's ratio	1.02

Evaluation of capsules

Weight variation

The uniformity of dosage units may be demonstrated by determining weight variation and/or content uniformity. The weight variation method is as follows.

Ten capsules are individually weighed and the contents removed. The emptied capsules are individually weighed and the net weight of the contents calculated by subtraction. From the results of an assay performed as directed in the individual monograph, the content of active ingredient in each of the capsules is determined.

Table 16: Weight variation of all formulations of F1-F7

S.No	Parameter	F1	F2	F3	F4	F5	F6	F7
1	Weight variation in mg	202.4	198.6	202.8	199.2	200.6	199.4	200.8

Lock length

It was tested by using vernier calipers.

Table 17: Lock length of all formulations F1-F7

S.No	Parameter	F1	F2	F3	F4	F5	F6	F7
1	Lock length	5.9	5.5	6.6	5.8	6.2	5.6	5.8

.

Moisture permeation test

Table 18: Moisture content values of all formulations F1-F7

S.No	Parameter	F1	F2	F3	F4	F5	F6	F7
1	Moisture content	3.2%	2.9%	3.2%	3.6%	3.3%	2.9%	1.75%

Assay

Table 19: Assay values of all formulations F1-F7

S.No	Parameter	F1	F2	F3	F4	F5	F6	F7
1	Assay in %	99.8	100	99.8	99.24	100.6	98.4	99.5

Content uniformity

Table 20: Content uniformity percentage of formulations F1-F7

S.No	F1	F2	F3	F4	F5	F6	F7
Strength 75mg	109.9%	108.7%	105.0%	102.5%	104.2%	95.7%	99.2%

Disintegration test

Table 20: Disintegration values of all formulations F1-F7

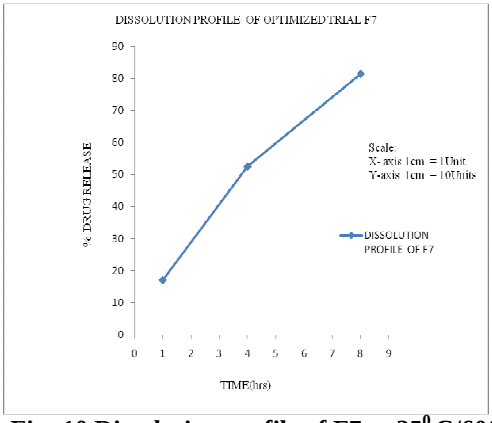
S.No	Parameter	F1	F2	F3	F4	F5	F6	F7
1	Disintegration time in min.	4.30	4.50	4.40	5.10	4.50	4.50	4.55

Stability Data

Stability studies are carried out as per ICH guidelines for F7 batch of this product at long term, Intermediate and Accelerated storage conditions. Stability data is used for evaluating the formulation and there is no change in the assay, disintegration time, dissolution profiles are observed.

Evaluation parameter values at different temperature conditions:

Dissolution profile of optimized batch F7 at 25°C±2ºC/60% ± 5% RH. Invitro dissolution profile of F7 at 25°C/60% RH



Time (Hrs)	Percentage of Drug release at 25°C±2ºC/ 60% ± 5% RH
1	17.1
4	52.5
8	81.4

Fig: 10 Dissolution profile of F7 at 25^0 C/60% RH

Dissolution profile of optimized batch F7 at 30°C±2ºC/65% ± 5% RH. Invitro dissolution profile of F7 at 30°C/65% RH

Time (Hrs)	Percentage of Drug release at 30°C±2ºC/ 65% ± 5% RH
1	17.1
4	52.4
8	81.4

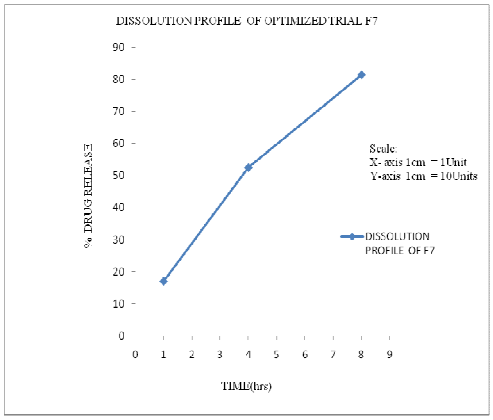
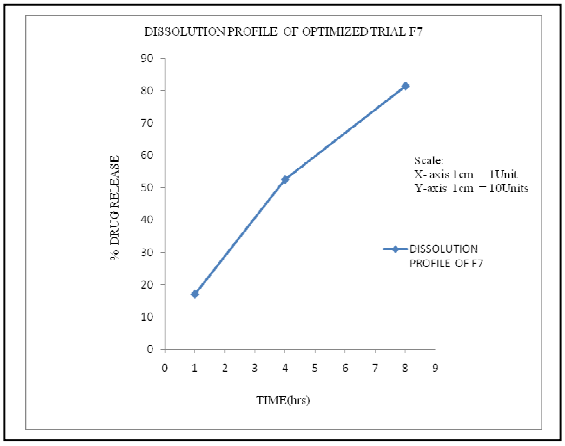


Fig 11: Dissolution profile of F7 at 30^0 C/65 % RH

Dissolution profile of optimized batch F7 at 40°C±2ºC/ 75% ± 5% RH. Invitro dissolution profile of F7 at 40°C/75% RH

Time (Hrs)	Percentage of Drug release at 40°C±2°C/ 75% ± 5% RH
1	17.1
4	52.4
8	81.4



After filling of pellets into capsule the parameters of capsules is observed.

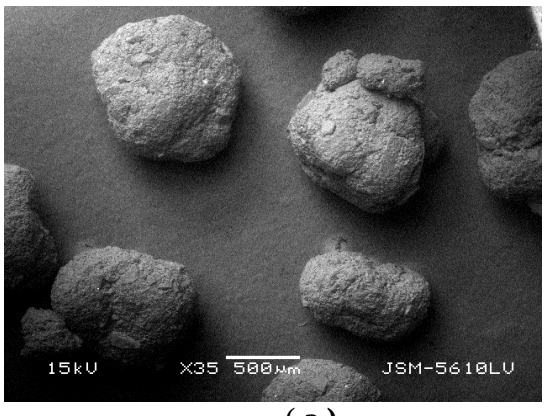
Capsules specification parameters

Parameters	Results
Strength	75mg
Description	Size '4' hard gelatin capsules, with white transparent body and pink cap containing white to off white spherical pellets of #20-24# size.
Capsule size	4
Weight of 10 filled capsules (gm)	2.004
Weight of individual capsules (mg)	200.2,198.8,201.6,200.8,199.4,202.4,198.6,202.8,199.2,200.6
Locked length (mm)	6.2,5.8,6.4,5.8,5.6,5.9,5.8,6.6,5.8,6.2

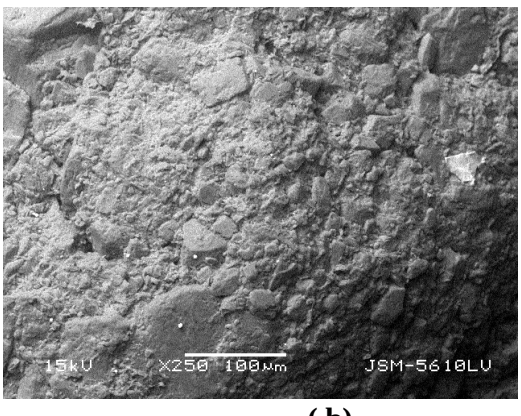
The shape of the pellets is not uniform. During drug loading temperature was maintained below 22ºC. The pellets size and strength is good. The size and strength of the pellets are good.

Scanning Electron Microscopy

The scanning electron microscopy (SEM) photographs showed that uniform pellets of Ambroxol were formed.



(a)



(b)

SEM photographs of F7 formulation a) pellets b) surface of the pellet

CONCLUSION

The active pharmaceutical ingredient Ambroxol was subjected to preformulation study, which encompasses the "Accelerated drug excipient compatibility study", and the results obtained with selected excipients showed good compatibility with Ambroxol.

Ambroxol coated pellets were formulated by using commercially available pellets and Ambroxol coated pellets were filled by capsule filling machine.

The stability of the capsules and pellet was determined by conducting "Accelerated stability testing" in 40°C ± 2°C / 75% ± 5%RH, 30ºC ± 2 ºC/ 65% ± 5% RH and 25±2°C/60±5% RH conditions for 1 month. Finally, after the duration, the product was analyzed for content and dissolution study. By the stability studies, the formulated Ambroxol modified release capsules and pellets proved to be stable throughout the period of the storage.

The Ambroxol modified release pellets were loaded in size 4 capsules. It showed good results in formulation of stable dosage. Marketed product for Ambroxol modified release, till date, has not been available. Modified release pellets have minimum volume in size, greater surface area and more surface 6 of disintegration time for pellets in capsules. Small volumes of pellets enter into the systemic circulation very fast. Moreover no accumulation of drug in the body occurs. Finally it is concluded that modified release pellets in capsule have more drug release rate.

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