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Formulation and Evaluation of Fast Dissolving Oral Film of Dicyclomine as potential route of Buccal Delivery

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Abstract

Buccal delivery is considered to be an important alternative to the peroral route for the systemic administration of drugs, as it considered the most convenient, easy, safest route of administration. Oral mucosa has rich vasculization, offers better permeability to many drugs & it act as an excellent site for the absorption of drugs. Fast dissolving oral film (FDOF) is used as a novel approach, as it dissolve rapidly in mouth and directly reaches to the systemic circulation. Oral film technology fulfills all the requirements of potential solid dosage form. The aim of this study is to formulate and evaluate the (FDOF) of an anticholinergic drug (Dicyclomine) and improved bioavailability of drugs as compared to conventional solid oral dosage forms. Oral films were prepared by using HPMC (hydroxypropylmethylcellulose), PVA (polyvinylalcohol), Eudragid RL-100, combination of two polymers and other excipients. Films were prepared by the solvent casting method. Films were evaluated for mechanical properties, Morphology study, swelling properties, disintegration time, dissolution time and in-vitro drug release. X1 formulation shows maximum in-vitro drug release 93.88%, following first order kinetics (r^2 =0.9915). The release exponent 'n' was found to be for X1 is 0.4487, which appears to indicate a Fickian diffusion and may indicate that the drug release was controlled by first order release.

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Key words:
FDOF, Dicyclomine, HPMC, PVA, Eudragid RL-100, solvent casting method.

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INTRODUCTION

Recently Fast dissolving technology have been emerges out as a new drug delivery system that provides a very convenient means of taking medications and supplements.[1] Fast-dissolving drug-

delivery systems were first developed in the late 1970s as an alternative to conventional dosage forms for pediatric and geriatric patients who experience difficulties in swallowing traditional oral solid-dosage forms. The buccal cavity is an attractive route of administration for Systemic drug delivery. Oral mucosa has a rich vascularization and offers higher permeability to many drugs. It has been well known that after buccal and sublingual administration drug solutes are rapidly absorbed in to the reticulated vein and are then drained into the systemic circulation[2].The concept of Fast Dissolving Drug Delivery System emerged from the desire to provide patient with a conventional mean of taking their medication. Difficulty in swallowing (Dysphagia) is a common problem of all age groups, especially elderly and paediatrics, because of physiological changes associated with these groups of patients[3]. Dicyclomine hydrochloride is tertiary amine, an anticholinergic drug. It exerts some nonspecific direct relaxant effect on smooth muscle. So used as an antispasmodic. In therapeutic doses they decrease spasm of the gastrointestinal tract, biliary tract, ureter and uterus. The half life of dicyclomine HCL is 4-6 hr. The drug is orally administered as 20 mg tablets twice daily with total daily doses ranging from 20 to 80 mg.

Following oral administration, Dicyclomine HCL is well absorbed (based on absorption of radiolabeled dicyclomine) and undergoes substantial first-pass metabolism; the systemic bioavailability of dicyclomine HCL is approximately 60%. In view of these facts this drug can be considered as a suitable candidate for fast dissolving oral film. In this study, an attempt is made to investigate the feasibility of fast dissolving oral films as a medium for the fast delivery of dicyclomine HCl with better bioavailability and enhanced patient compliance.

Material and methods

Materials

Dicyclomine was purchased from Jackson Laboratories Pvt Ltd, Amritsar, India. HPMC-15, PVA were purchase from central drug house Eudragit RL- 100 and Aspartame were obtained as a gift sample from Ranbaxy Pvt Ltd, gurgaon. Organic solvents used were of analytical grade and other chemicals of Laboratory grade.

Preparation of films

Preparation of Polymeric films of and Hydroxypropylmethyl cellulose (HPMC) and PVA:

Drug (dicyclomine HCL) containing fast dissolving films were fabricated by the solvent casting method. The optimized amount of polymer PVA(2.5%w/v) was dissolved in 5ml of water and stirrer continuously for 1 hour, optimized amount of sweetener, and Plasticizer were dissolved in 95% ethanol and then added to the polymeric solution, flavor and were dissolved in 2 ml distilled water and added to the polymeric solution. The optimized amount of drug was dissolved in 2ml of water and kept on sonication for proper dispersion. The drug solution was then added to the polymeric solution was stirred for 30 min using magnetic stirrer and was kept in undisturbed condition till the entrapped air bubbles were removed. The aqueous solution was casted in a plastic petridish having 68 cm^2 surface area and was dried at controlled room temperature (25° - 30°C, 45 %RH) as well as at increased temperature (microwave oven). The film took approximately 48 hr to dry at controlled room temperature. The dried film was carefully removed from the petridish and was cut into size required for testing. The films were stored in air tight plastic bags till further use[4, 5]. Same procedure were be followed for the preparation of HPMC-15 film and combination of HPMC15:PVA (1:1.5%w/v) and HPMC-50 : Eudragid(2:1%w/v). The composition of drug loaded film is shown in table no. 2.

Evaluation of prepare fast dissolving oral films:

Film Thickness:

The thickness of each of 10 film of each type of formulation was measured using a micrometer screw gauge[6] and the average was determined as shown in Table no. 3

Weight Variation:

The individual weight each of 10 samples of each formulation was determined. The average weight was calculated as shown in table no. 3.

Hydration Study (water uptake/ swelling study) [7, 8] The film sample was weighed and placed on a preweighed stainless steel wire mesh. The wire mesh was then submerged in a petridish containing 20 ml distilled water. Increase in weight of the film was determined at regular time intervals until a constant weight was obtained as shown in table no. 3. The hydration ratio of the film was calculated using following formula-

$$\text{Hydration ratio} = \frac{W_t - W_o}{W_o}$$

Where Wt = weight of film at time t and W_o = weight of film at zero time.

Moisture Loss (Moisture Vapor Transmission) [9]

The percent moisture loss was determined by placing prepared film in desiccators containing anhydrous calcium chloride. After three days, the film was taken and reweighed. The percent moisture loss was calculated using following formula results are in table no. 2

$$\text{Moisture loss} = \frac{W_o}{W_o - Wt} \times 100$$

Where W_o= initial weight W_t = final weight.

Measurement of Mechanical Properties [10, 11]

The tensile testing gives an indication of the strength and elasticity of the film, reflected by the parameters - tensile strength, elastic modulus, % strain, and load at yield. The type of the polymer is characterized by following table:

Table: 1 Mechanical Properties of Film

Type of polymer	Tensile Strength	Elastic Modulus	% Strain
Soft and Weak	Low	Low	Low
Hard and Brittle	Moderate	High	Low
Soft and Tough	Moderate	Low	High
Hard and Tough	High	High	High

The mechanical properties of the film gives idea about to what extent the film can withstand the force or stress during processing, packaging, transport and handling. The desirable characteristics of film are moderate tensile strength, low elastic modulus, high % strain and high load at yield. From the above table, the polymer should give soft but tough film.

Percent Elongation

The prepared film was pulled by means of a pulley system. Weights were gradually added to the pan to increase the pulling force till the film was broken. The elongation was determined by noting the distance travelled by pointer before break of film on the graph paper.[12, 13] The percent elongation was calculated by using formula-(mm^{-2}) as given below, and the results are shown in table no. 4.

$$\text{Percent elongation} = \frac{L_1}{L_o} \times 100$$

Where L_1= increase in the length, L_o = Initial length.

Tensile Strength:

Film strip of dimension 2 X 2 cm^2 and free from air bubbles or physical imperfections was held between two clamps positioned at a distance of 3 cm apart. A cardboard was attached on the surface of the clamp via a double sided tape to prevent the film from being cut by the grooves of the clamp. During

measurement, the strips were pulled at the bottom clamp by adding weights in pan till the film breaks[14]. The force was measured when the films broke results is shown in table no.4

$$\text{Tensile strength (kg/mm}^2\text{)} = \frac{\text{Force at Break}}{\text{Initial cross sectional area of the film (mm}^2\text{)}}$$

Folding Endurance

This parameter was determined by repeatedly folding one film at the same place till it broke. The number of times the film could be folded at the same place without breaking/cracking gave the value of folding endurance as shown in table no. 4.

Surface pH:

The surface pH of the films was determined in order to investigate the possible side effects due to change in pH *in vivo*, since an acidic or alkaline pH may cause irritation to the buccal mucosa. The film to be tested was placed in a Petri dish and was moistened with 0.5 ml of distilled water and kept for 1 h. The pH was noted after bringing the electrode of the pH meter in contact with the surface of the formulation and allowing equilibrating for 1.0 min.[15] The average of three determinations for each is shown in Table 4.

Compatibility studies:

The drug-polymer compatibility was confirmed by taking IR spectrum and DSC thermogram of drug, polymer and physical mixture of drug-polymer proved that the excipients were compatible with the Dicyclomine as shown in figure: 4, 5, 6, and 7

Drug Content and Content Uniformity:

The drug content and content uniformity test was performed to ensure uniform distribution of drug. Five film units (2 cm x 2 cm) were cut from the four corners and the central part of the film (n=3). Each film unit was placed in 100 ml of distilled water. Samples of 10 ml were withdrawn and diluted with 25 ml of methyl orange (1%w/v) and extracted with chloroform (3x7.5 ml), and then the volume of sample was made up to 50 ml with sodium acetate solution. The solutions were filtered and analyzed at 465nm in a UV-Visible Spectrophotometer (Model UV-1700, Pharmaspec, UV-Visible Spectrophotometer, Shimadzu, Japan). The average of five films was taken as the content of drug in one film. The concentration of Dicyclomine HCL (in µg/ml) was calculated using standard calibration curve of dicyclomine. Content uniformity of films were done by selecting randomly five 4cm^2 films from different batches and performing study same as drug content results is shown in table no. 3.

In vitro Disintegration and Dissolution Time :(Chen MJ et al, 2006)

The disintegration time is the time when a film starts to break or disintegrate. The dissolution time is the time when the film completely dissolves. The *in vitro* disintegration and dissolution time of fast-dissolving films was determined visually in a glass dish of 25 ml distilled water with swirling every 10 s. Disintegration and dissolution time was measure results are shown in table no. 3.

In Vitro Dissolution Study (drug release rate study): (Cilurzo F, et al, 2008)(Perumal VA, et al 2008)

The *in vitro* dissolution test was carried out in a USP II paddle dissolution apparatus. Samples of Dicyclomine-loaded films were equivalently containing 20 mg (4cm2) was cut and placed in dissolution media. The dissolution medium consisted of 300 ml freshly deionized simulated saliva (pH 6.8), maintained at 37 ± 1 ^{0}C and stirred at 100 rpm. Samples of 10 ml were withdrawn at predetermined time intervals & replaced with fresh medium. The samples was diluted with 25 ml of methyl orange (1%w/v) and extracted with chloroform (3x7.5 ml), and then the volume of sample was made up to 50 ml with sodium acetate solution. The solution was filtered using Whatman filter Paper. The absorbance was taken at 465 nm against blank UV spectrophotometer (UV1700, Shimadzu, Japans) results are shown in figure: 2.

RESULTS AND DISCUSSION

Preparation of film formulations:

All the film formulations containingHPMC-15, PVA and combination of HPMC-15: PVA, HPMC-50: EudragitRL-100 polymer with propylene glycol as plasticizer were readily prepared by solvent casting. A solvent mixture of ethanol and water was required to keep both polymers in solution

Evaluation of Prepared Films:

From the results of the tests for physical characterization conducted, it is observed that the weight and thickness of all film samples was uniform within each formulation.

Films formulated from PVA were smooth, flexible and transparent whereas those prepared from HPMC-15 were slightly rough in texture, less flexible and translucent. While the film prepared from combination of HPMC -15: PVA and HPMC-50: Eudragid RL-100 were smooth in texture, flexible and slightly translucent. All film formulations exhibited good folding endurance exceeding 500, except X2 formulation indicating that they are tough and flexible.

Surface pH

An acidic or alkaline pH of administered dosage forms can irritate the buccal mucosa. The measured surface pH was found to be close to neutral in all the formulations which means that they have less potential to irritate the buccal mucosa and therefore they should be fairly comfortable.

Drug content

All the film formulations of Dicyclomine HCL containing polymers show uniform drug content as seen in Table no.3

Swelling Index

The measurement of Swelling Index indicates that maximum swelling takes place in the formulations containing higher proportions PVA namely X1 and the least in those containing combination of HPMC-50 and Eudragid RL-100, because Eudragid RL-100 is water insoluble and less hydrophilic and therefore subject to lesser swelling upon hydration. It was also observed that films containing the hydrophilic polymers disintegrated very fast. The presence of the hydrophilic polymer, PVA seems to increase the surface wettability and swelling of the films. The rank order of swelling index from films was found to be X1>X2>X4>X3.

In vitro drug release studies

In vitro drug release studies in simulated saliva show more than 85 % release of dicyclomine HCL from all film formulations, *i.e.*, X1, X2, X3, and X4 with in 5 minutes with X1 showing a maximum percentage drug release of 94 %. This could be attributed to the higher rate and extent of swelling of the larger proportion of the hydrophilic polymer, PVA. The rank order of in vitro drug release from films was found to be X1>X3>X4>X2.

Kinetic analysis of *in vitro* release data:

In order to determine the release mechanism that provides the best description to the pattern of drug release, the *in vitro* release data were fitted to zero-order, first-order, Hixson Crowell equation and Higuchi matrix model. The release data were also kinetically analyzed 15 using the Korsmeyer–Peppas model. The release exponent (n) describing the mechanism of drug release from the matrices was calculated by regression analysis using the following equation.

$$Mt/ M_{\infty} = Kt^{n}$$

Where Mt/M_{∞} is the fraction of drug released.

When the release data were fitted to Koresmeyer-Peppas release model and interpretation of release exponent values (n) enlightens in understanding the release mechanism from the dosage form[19].

Release exponent (n)	Drug transport mechanism
0.5	Fickian diffusion
0.5< n <1.0	Non- Fickian diffusion
1	Case-II transport
1 >	Super Case-II transport

After undergoing the release model for all the formulations the in vitro drug release of the optimized formulation X1 was best explained by first order, as the plots showed the highest linearity (r^2 = 0.9915), followed by Korsmeyer peppas (r2=0.9771), Higuchi (r^2 = 0.9602) and then zero order (r^2 = 0.8676). The corresponding plot (ln Mt/M∞ vs ln time) for the Korsmeyer-Peppas equation of the optimized formulation X1 indicated good linearity for X1 formulation. The release exponent 'n' was found to be for X1 is 0.4487, which appears to indicate Fickian diffusion and may indicate that the drug release was controlled by first order release.

Stability studies:

When the oral film preparation was stored in an aluminium package under normal condition or in a chamber controlled at 40°C and 75% in humidity for 4–13 weeks, no apparent changes in the dicyclomine content, form or color of preparations were observed. The contents of dicyclomine were fairly stable ranging from 98.4% to 101.7% during 13 weeks after storage at 30°C and 60% humidity (normal condition), or from 98.0% to 100.4% during the same periods after storage at 40°C and 75% RH humidity (accelerated condition).

CONCLUSION

This study shows that it is possible to formulate fast dissolving films of dicyclomine HCL with the intention of obtaining better therapeutic efficiency with increasing bioavailability and improving patient compliance. Plasticizer used PEG-400 resulted in better films in respect to physicochemical parameter like, tensile strength, % elongation, folding endurance and flexibility. Aspartame used as a sweetener will successfully mask the bitter taste of the drug dicyclomine. Formulation X1 shows minimum disintegration and dissolution time in comparison to other formulation. X1 was the best formulation showed 94.1376% drug release in 5 min. Data obtained from correlation coefficient and slope values revealed that drug release from formulation followed first order kinetics. *In vitro* stability evaluation of optimized formulation X1 with different environmental conditions, confirms the potential of films for longer storage.

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Table 2: Composition of Drug loaded fast dissolving film

Ingredients	X1	X2	X3	X4
Dicyclomine HCL(mg)	251	251	251	251
PVA(mg)	250	-	-	-
HPMC-15	-	200mg		-
HPMC-50:Eudragid	-	-	200:100mg	-
HPMC-15:PVA	-	-	-	100:150mg
PEG-400	300	300	300	300
Aspartame	62.52	62.52	62.52	62.52
citric Acid	15	15	15	15
Menthol	0.029	0.029	0.029	0.029
Tween -80	0.2ml	0.2ml	0.2ml	0.2ml
Water(ml)	10	10	10	10
Ethanol	q.s	q.s	q.s	q.s

Table 3: Evaluation of mouth dissolving film of Dicyclomine HCL

Evaluation Parameters	Thickness (mm)	Mean weight (mg)	Drug content %	% moisture absorption	% Moisture loss
X1	0.150±0.002	119.6±1.52	106±0.002	1.51±0.004	1.423±0.003
X2	0.170±0.002	122.3±3.05	95±0.004	1.43±0.005	2.201±0.005
X3	0.175±0.001	127±7.2	97±0.006	2.31±0.001	2.882±0.002
X4	0.155±0.002	125.6±2.5	99±0.005	2.038±0.007	1.976±0.006

Table 4: Evaluation of mouth dissolving film of Dicyclomine HCL

Evaluation Parameter	Tensile strength Kg/mm²	% Elongation	Folding Endurance	Disintegration time (sec)	Dissolution time (sec)	Surface pH
X1	1.283±0.231	65.12±1.6	>800	14	140	6.4±0.13
X2	1.135±0.004	22.9±0.58	200	37	168	6.6±0.16
X3	1.286±0.037	36.2±1.67	>800	24	127	6.5±0.18
X4	1.393±0.091	40.7±1.42	600	24	129	6.4±0.15

Table 5: Drug release kinetics of formulation

Formulation	Zero order		1st order equation		Higuchi Equation		Korsmeyer Peppas's Equation	
	k	R^2	k	R^2	n	R^2	K	R^2
X1	0.2359	0.8676	0.0039	0.9915	5.3142	0.9602	0.4483	0.9771
X2	0.2152	0.846	0.0027	0.9529	4.8675	0.9463	0.453	0.971
X3	3.61	0.8654	-0.0032	0.9757	5.1785	0.9579	0.4577	0.9789
X4	0.2368	0.812	-0.0037	0.9693	5.1759	0.9579	0.4778	0.9547
Best fit model	First order		Peppas model		Peppas model		First order	

R^2 =coefficient of determination: K=rate constant

Figure 1: Disintegration and dissolution time study of X1-X4 film formulations

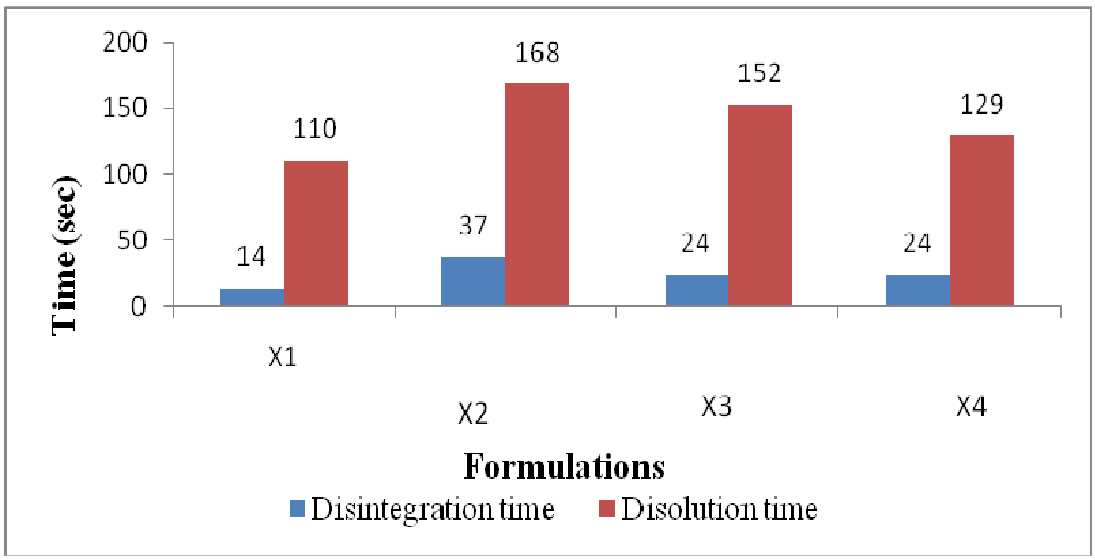


Figure 2: In vitro Release profile of Dicyclomine HCL film formulation X1-X4.

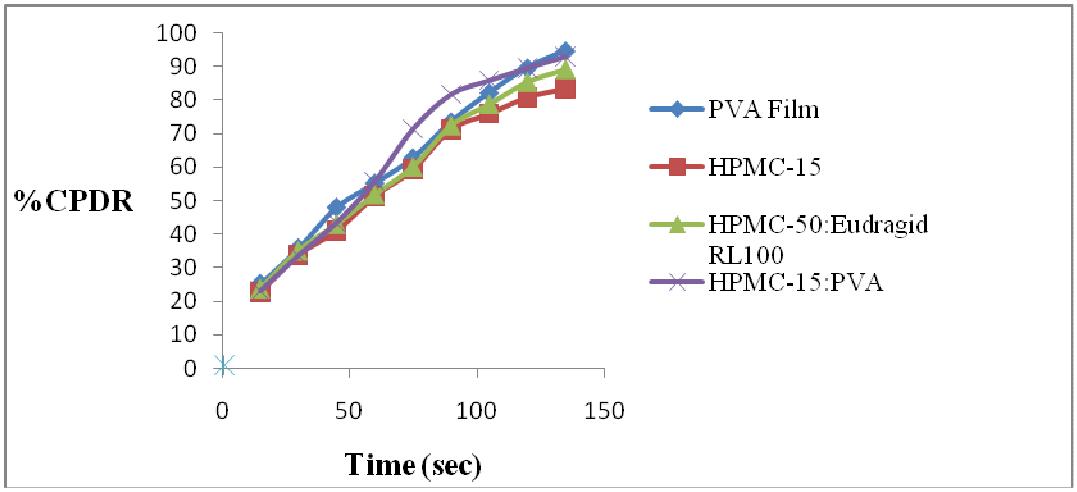


Figure 3: Comparison of in- vitro drug release of X3 formulation after 90 days storage

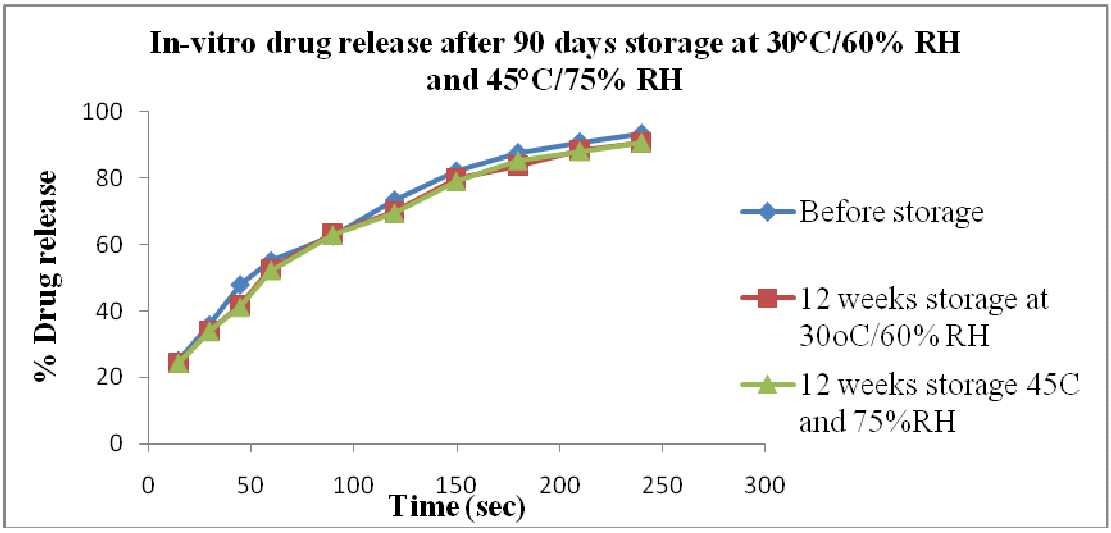


Figure 4: IR spectroscopy of drug and poly vinyl alcohol (PVA)

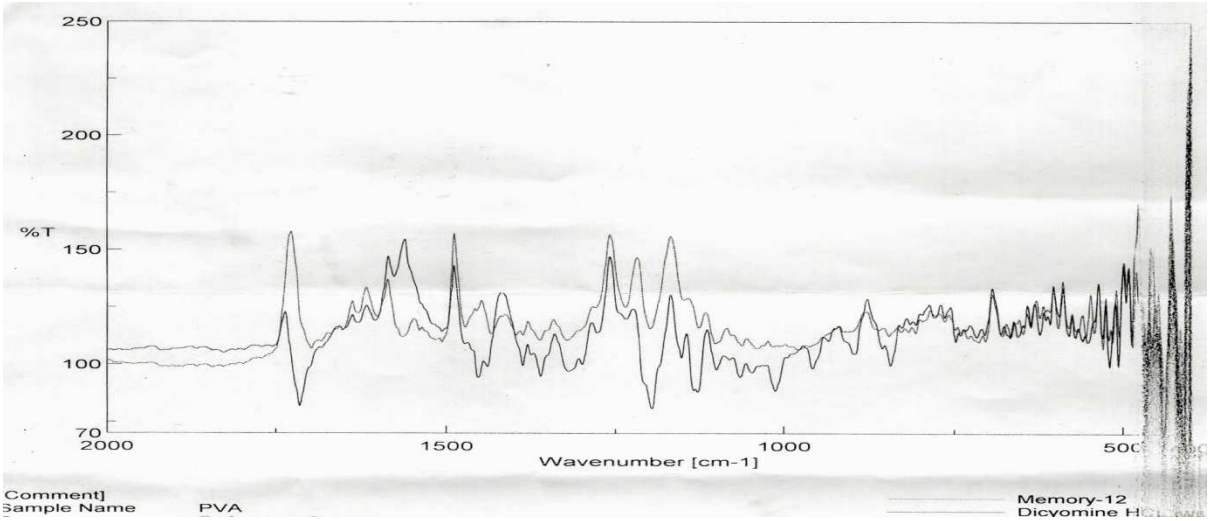


Figure 5: IR spectroscopy of drug and HPMC-15

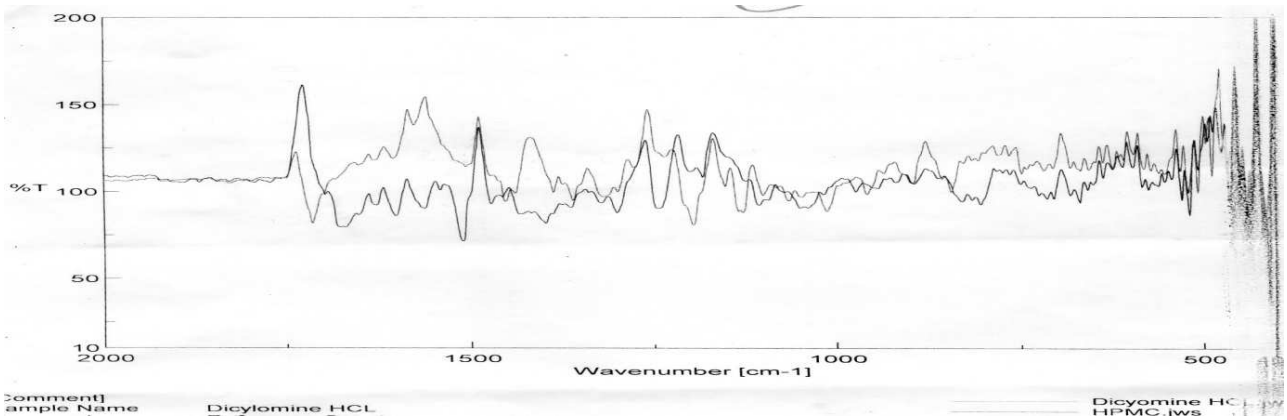


Figure 6: DSC thermogram of drug and polymers (HPMC, PVA)

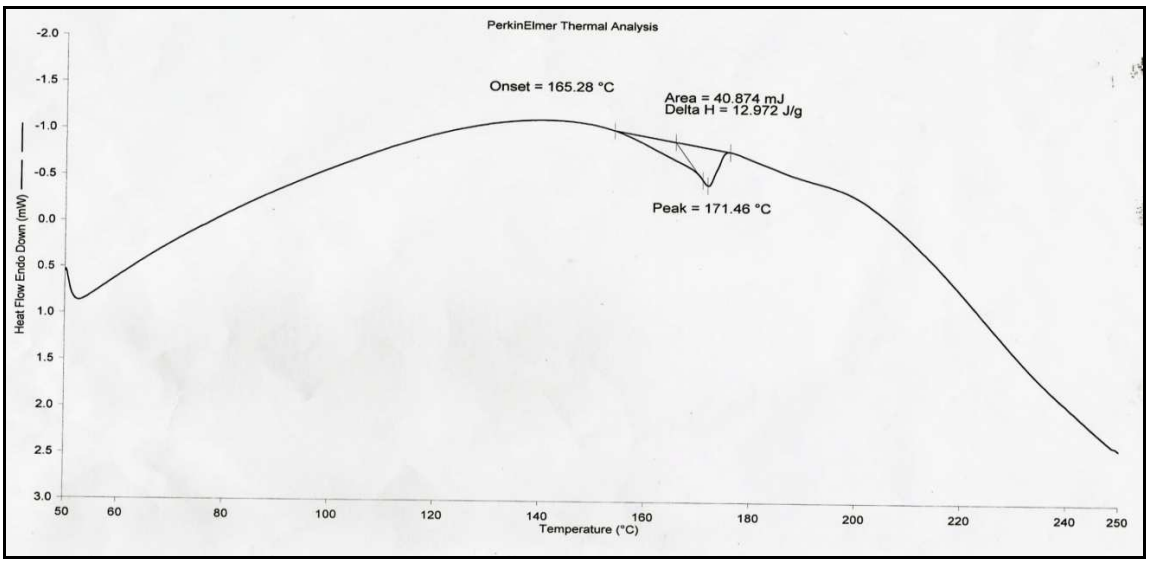
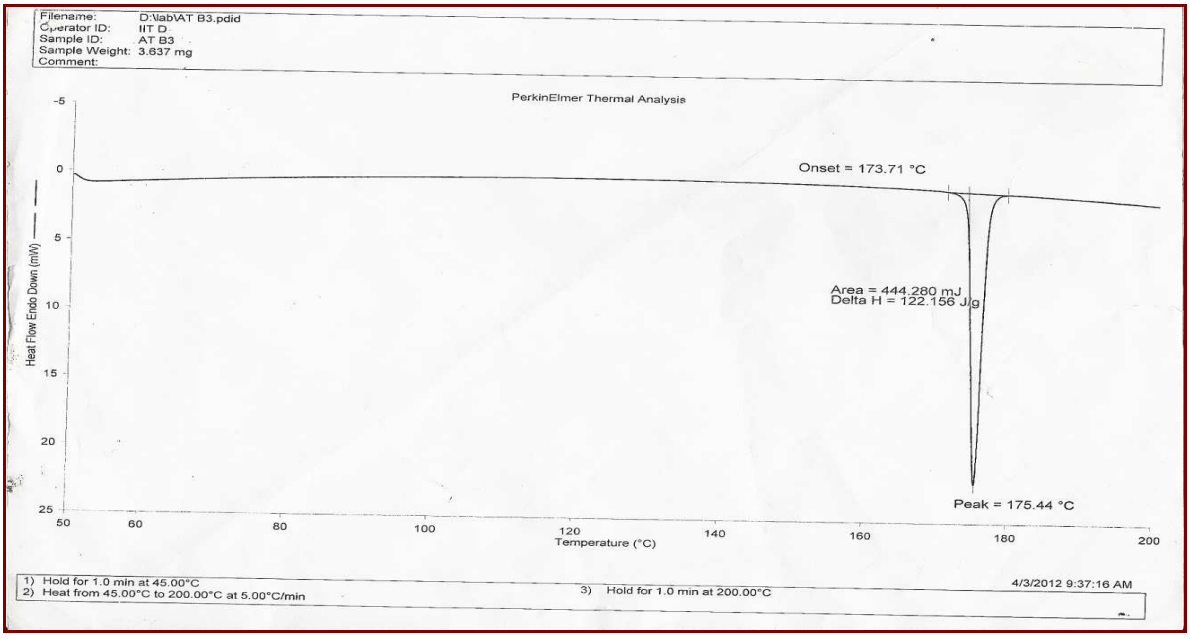


Figure 7: DSC thermogram of dicyclomine HCL



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