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Research Article **Novel drug delivery system**

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DEVELOPMENT AND EVALUATION OF A SUSTAINED RELEASE MICROENCAPSULES OF METFORMIN HYDROCHLORIDE

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ABSTRACT

A sustained release dosage form of Metformin HCl in the form of microspheres was prepared by the solvent evaporation method. Solvent evaporation method was attempted in both aqueous as well as oily manufacturing vehicles. Different polymers such as Ethyl Cellulose, *Eudragit® RS PO, Eudragit® RL PO, Eudragit® S 100, Eudragit® RL 100* and different combinations of these polymers were tried and the resulting microspheres were evaluated for entrapment efficiency, drug loading and percent yield of the process and dissolution profile. The combination which showed the desired characters was chosen and further compared with a marketed formulation. The aim was to develop a multiparticulate sustained release drug delivery system to be converted to a liquid oral formulation, so that patient suffering from dysphagia, stroke, difficulty in swallowing, geriatric patients etc. may consume it easily and long term therapy may be maintained as required in patients suffering from osteoarthritis, diabetes.

KEYWORDS: **Metformin HCl, Ethyl Cellulose, *Eudragit® S 100, Eudragit® RL 100,* Sustained release, solvent evaporation**

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INTRODUCTION

Much of the research efforts in developing novel drug delivery systems have been focused on per oral sustained or controlled-release dosage forms. Among the oral dosage forms, multiunit formulations such as micro particles have become more popular because of their advantages over single unit dosage forms. They may be spread out more uniformly in the gastrointestinal tract leading to more uniform drug absorption, reduced local irritation, and decreased retention of polymeric materials (1, 2). They have been reported to be relatively unaffected by digestive tract activities, causing less variation in the results of pharmacokinetic studies (3). Attention has been recently devoted to liquid sustained release preparations that are more palatable to paediatric and convenient to geriatric patients (1, 4). This formulation may also help in giving drug delivery to patients suffering from dysphagia; stroke where consuming a tablet will be very difficult. This problem becomes more acute for the administration of sustained action dosage forms due to the increase in the volume of the delivery system and necessity to take it intact without breaking. Formulating such systems as a suspension presents a novel means of circumventing the potential problems associated with the administration of such system (5, 6). Multiparticulate systems could also be formulated as liquid suspensions allowing ease of swallowing and flexibility in the dose adjustment for pediatric and geriatric patients (2). Many techniques for the preparation of micro capsules have been developed and reviewed (7).

MATERIALS & METHODS

Drug: Metformin Hydrochloride was a gift sample from Aarti Drugs, Mumbai.

Excipients: Ethyl Cellulose, Eudragit® RS PO, Eudragit® RL PO, Eudragit® S 100, Eudragit® RL 100 were received as a gift sample from Evonik Industries.

As the drug was highly water soluble, a non-aqueous method was selected for preparation of the microcapsules. For the efficient multiparticulate formulation, such as gastro retentive sustained release floating microspheres, selection of appropriate encapsulation material is very important. Ethyl cellulose (EC) is a water insoluble polymer, and widely used in pharmaceutics as a coating material for sustained-release microcapsules. This is due to its high safety, good stability, easy fabrication and cost efficiency.(11) Therefore ethyl cellulose was selected as a model encapsulation material for preparation of microspheres. Eudragit® RSPO is insoluble in water and digestive juices, but it is permeable and swells in solution. In combination with ethyl cellulose, Eudragit® RS PO was used to control the release rate of drug. (12,13) Eudragit® RLPO is a copolymer of ethyl acrylate, methyl methacrylate and a low content of methacrylic acid ester with quaternary ammonium groups. The ammonium groups are present as salts and make the polymers permeable. Eudragit® RLPO is used, as its insoluble in dissolution medium, highly permeable and offers pH independent swelling. Its useful for time controlled release. Eudragit® RL100 can be used for targeted drug release as its insoluble, high permeability and pH independent swelling. Customized release profile by a combination of RL and RS grades in different ratios can be achieved. The polymer gives Suitable for matrix structures. Eudragit® S100 can be used for granulation of drug substances in powder form for controlled release. It is effective and forms a stable enteric coating with a fast dissolution in the upper Bowel. The polymer provides site specific drug delivery in intestine by combination with EUDRAGIT® S grades. The polymer can show variable release profiles.

METHODS

1.1 EXPERIMENTAL

Aim of the formulation development was to develop sustained release microspheres of Metformin HCl, with optimum yield, encapsulation efficiency. The criterion for drug release was set as a sustained release of drug from the microspheres for about 12 hrs and comparable with the marketed formulation. Various formulation trials were carried out aiming to produce desired formulation.

1.1.1 Trials using solvent diffusion-evaporation method with combination of polymers

Various formulation trials were carried out to check the efficacy of solvent diffusion-evaporation method in preparation of microspheres. Different trials were carried out using solvent diffusion-evaporation method as shown in Table 1. Attempts were made to formulate Metformin HCl microspheres using Eudragit® polymers and ethyl cellulose by solvent diffusion-evaporation method. Various batches were formulated using these polymers in combination with an objective to achieve sustained release of drug for about 12 hrs.

Selection of Drug Polymer Ratio

The drug to polymer ratio was selected to be 1:2 for all the trials. The ratio was selected after running trials at different drug polymer ratios of 1:1, 1:2, 1:3. The batches of 1:1 were unable to give a sustained release of the drug. The batches of drug to polymer ration 1:3 resulted in batches giving very slow release of Metformin over an extended time span. The batches with a drug to polymer ratio of 1:2 were found to exhibit a sustained release profile in dissolution studies. It was also assumed that batches of drug to polymer ratio 1:2 were convenient for further optimization.

Table 1
Trials using different polymers or combination of polymers

Ingredients/ Parameters	Q1	Q2	Q3	Q4	Q5
Metformin HCl (g)	3	3	3	3	3
Ethyl cellulose (g)	*3*	-	*3*	*3*	*3*
Eudragit® RS PO (g)	*3*	*3*	-	-	-
Eudragit® RL PO (g)	-	*3*	-	*3*	-
Eudragit® S 100 (g)	-	-	*3*	-	-
Eudragit® RL 100 (g)	-	-	-	-	*3*
Acetone: Dichloromethane ratio	5:1	5:1	5:1	5:1	5:1
Volume of organic phase (ml)	30	30	30	30	30
Volume of oil phase (ml)	100	100	100	100	100
Oil Phase used	Liquid Paraffin	Liquid Paraffin	Liquid Paraffin	Liquid Paraffin	Liquid Paraffin
Stirring rate (rpm)	1200	1200	1200	1200	1200
Temperature (ºC)	RT	RT	RT	RT	RT

Procedure: For Microencapsulation using Oil Phase as Manufacturing Vehicle, the following procedure was followed

- For the preparation of microspheres by solvent diffusion-evaporation method the drug and polymers were added to the solvent mixer and dissolved to form homogenous polymer solution containing drug.
- Liquid Paraffin (continuous phase) was kept under mechanical overhead stirrer equipped with a four bladed with required stirring speed.
- The polymer solution was slowly introduced into Liquid Paraffin oil dispersion with the help of pipette by dipping it into the dispersion media. Then the emulsion formed was stirred for about 3 hrs, so that the organic solvents were diffused in to continuous phase and were evaporated.
- The microspheres formed were collected by filtration of continuous phase. The collected microspheres were washed with n-Hexane to remove non-encapsulated drug and then with warm distilled water to remove traces of n-Hexane and Liquid Paraffin oil.
- The collected microspheres were air dried 24 hrs.

Method of introducing polymer solution

Polymeric solution was introduced into the dispersion phase by using a pipette. Polymer solution was sucked in dry pipette. Then tip of pipette was inserted deep in dispersion phase and polymer solution blown out slowly inside. The contact of the polymer solution at the interface of dispersion phase and outer

environment was avoided. As soon as polymer solution contacts at the interface, the organic solvents like ethanol diffuses to water and air phase, causing the precipitation of polymer at the surface of dispersion phase forming film.
All the batches were evaluated for various properties.

1.2 EVALUATION OF MICROSPHERES

1.2.1 Particle Size and morphology evaluation: (16)

Optical Microscope was used to evaluate both the morphology and surface characteristics of the microcapsules.

1.2.2 Percent Yield(18)

Percent yield of microspheres was calculated by the formula,

$$\% \text{ Yield} = \frac{\text{Total weight of microspheres}}{\text{Total weight of drug, polymer and other excipients added}} \times 100$$

This parameter was helpful in choosing the preparation method of microsphere giving minimum losses and highest yield

1.2.3 Encapsulation efficiency (18)

The drug content of drug loaded microspheres was determined by dispersing 100 mg of microspheres in 80ml of phosphate buffer pH 6.8l followed by agitation with a magnetic stirrer to extract the drug for 24 hrs. After filtration through Whatman (0.45micron) filter paper, the drug concentration in the aqueous phase was determined by taking the absorbance of this solution spectrophotometrically at 233.2 nm. Eudragit® polymers and Ethyl Cellulose did not interfere under these conditions. Each determination was made in triplicate. The concentration of Metformin HCl in solution was calculated from the formula;

Concentration= (Absorbance-0.011)/0.0786

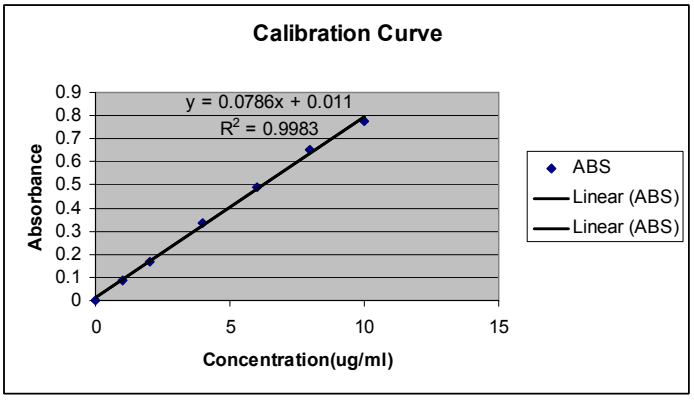

Figure 1
Calibration Curve of Metformin

Calibration Curve of Metformin From standard plot of Metformin HCl in phosphate buffer

Thus, the drug entrapped in 100 mg of microspheres was calculated, which is referred as “Percent drug loading” and further, total drug encapsulated in total recovered microspheres from the procedure is calculated. It was expressed in percentage called as “Percent drug encapsulation”. The experiment was done in triplicate and the average ± S.D was calculated.

1.2.4 Release kinetics (19)

A USP basket apparatus has been used to study *in-vitro* drug release from microspheres. A weighed amount of microspheres equivalent to 500 mg drug was placed in the basket. Dissolution medium used was phosphate buffer (pH 6.8, 1000 ml) and maintained at 37±0.5°C at a rotation speed of 100 rpm. Prefect sink conditions prevailed during the drug release studies. Five ml of sample was withdrawn at each 1, 2,3,5,6,8,10 & 12 hr interval. Sample was then passed through a Whatman filter paper (0.45micron), and analyzed spectrophotometrically at 233.2 nm to determine the concentration of drug present in the dissolution medium. . The volume was replenished with the same amount of fresh dissolution fluid each time to maintain the sink condition. Linear regression was used to analyze the *in-vitro* release mechanism. The experiment was conducted in triplicate and the average ± S.D was calculated.

1.3 RESULTS AND DISCUSSION

The microspheres possessed the thick shell with inside round cavity (micro balloons). The drug was dispersed in the matrix of this shell as shown in Figure 26. Formulated microspheres were the matrix device consisted of drug homogeneously dispersed throughout the polymer matrix. Shell consisted of the polymers Eudragit® and ethyl cellulose. The slow dissolution of the polymer created channels within shell, and drug gets dissolved in the dissolution medium in these channels. Concentration gradient of drug between microsphere shell and outer environment generated the flux of drug to the outside medium. After 12 hrs of dissolution study, the microspheres remained as a ghost matrix. This rigid matrix remained due to the insolubility of the ethyl cellulose in aqueous phase.

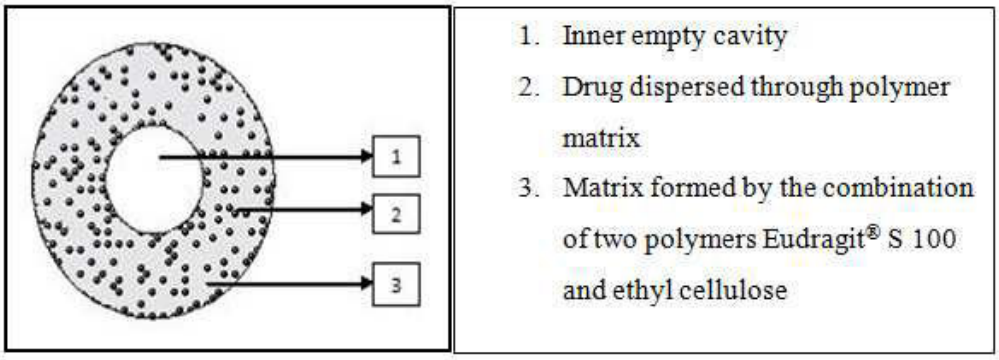

Figure 2

Solvent diffusion-evaporation method was employed in batches P6 and P7. Different Stirrer type was used to change stirring efficiency. Microspheres produced by using mechanical stirrer were found to be better than microspheres produced by using magnetic stirrer with respect to size, shape, yield and encapsulation.

1.3.1 Effect of various polymers or combination of polymers

Initially aqueous method was chosen to prepare microspheres, although the fact that Metformin HCl is a highly water soluble drug was know. It was considered that by adding NaCl entrapment efficiency of the drug could be improved. Result showed that aqueous method produced entrapment which was not acceptable practically. Later non aqueous method was selected and the entrapment efficiency drastically improved as Metformin HCl solubility is liquid paraffin was minimized and the polymer got sufficient time to coat the Metformin drug and encapsulate it.

Table 2
Effect of various polymers or combination of polymers over angle of repose, mean particle size, % entrapment, % yield

Parameter	Q1	Q2	Q3	Q4	Q5
Angle of repose	8.13°	28.2°	38.79°	24.52°	17.79°
Mean Particle size	140.45	196.54	200.87	154.87	159.05
% Entrapment	76.36364	76.36364	76.36364	76.36364	76.36364
% yield	80	80.33	100	84.11	82.78

Various polymers were evaluated for the sustained release profile of the drug, maintaining a drug: polymer ratio of 1:2. Q3 showed controlled release. Other batches Q1, Q2, Q4, Q5 failed to sustain the release of Metformin. It was observed that Q3 had better release profile compared to that of Q5. Thus Q3 was compared with the marketed formulation and it was observed that the F2 value was 57. (17)

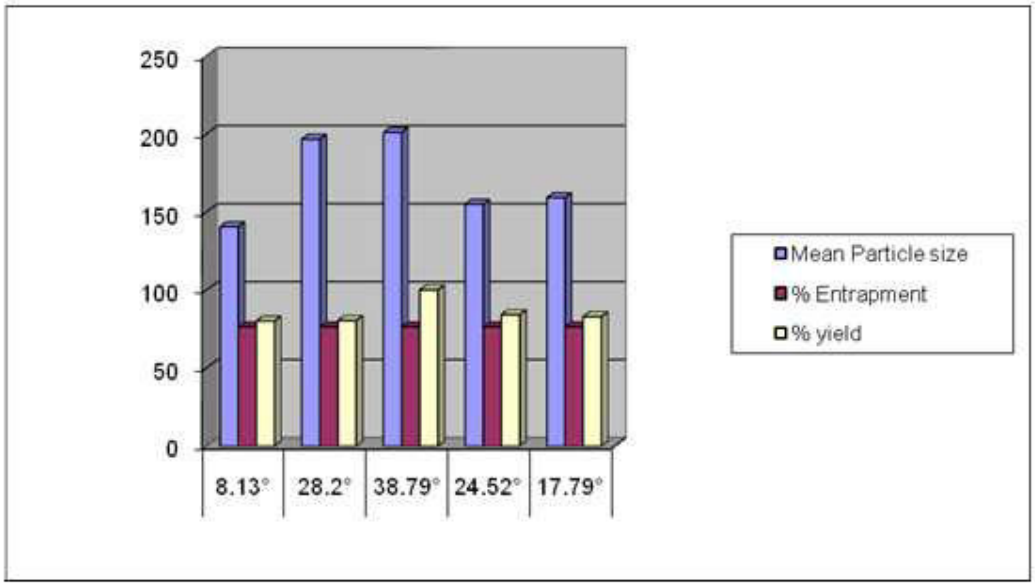

Figure3
Effect of various polymers or combination of polymers over angle of repose, mean particle size, % entrapment, % yield

Table 3
Release Profile of the formulation

Time	STD	Q1	Q2	Q3	Q4	Q5
2	31.87	109.11	64.83	24.33	103.07	111.62
8	81.98	108.15	110.67	56.05	105.89	105.89
16	89.53	118.73	112.69	87.26	109.66	107.15

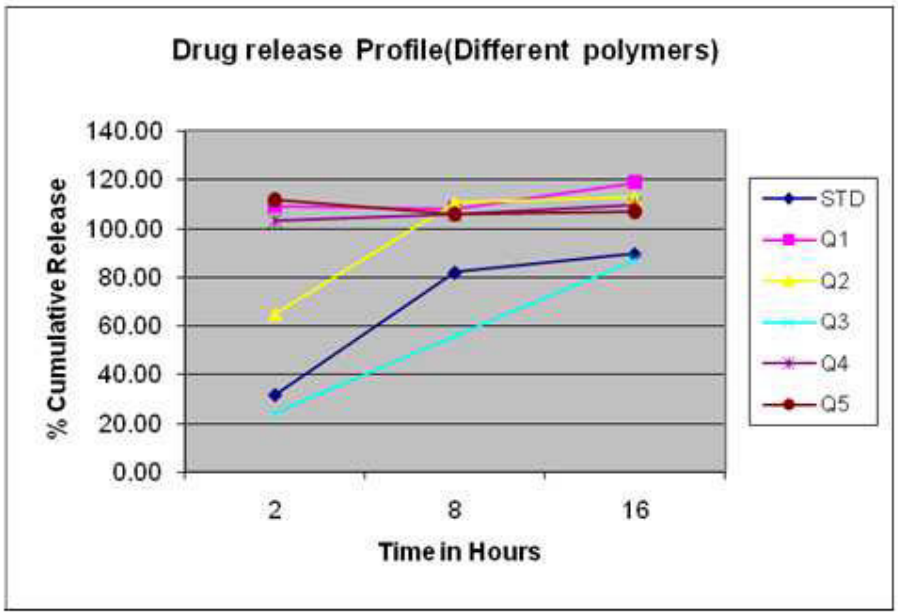

Figure 4
Release Profile of different formulation

1.4 OPTIMIZATION OF MICROCAPSULES

From the in vitro release profiles of all the batches of microcapsules prepared, Q3 i.e. Ethyl Cellulose and Eudragit S100 (1:1) in ratio of 1:2 shows required rate of drug release. Also this batch showed encapsulation efficiency (21.815%) (Table 4), it stood well in all physical evaluation parameters. Hence this batch was selected for further studies.

1.4.1 Comparison of Q3 with marketed formulation

The release profile of Q3 was further compared with marketed formulation and a similarity factor F2 was calculated.

Table 4
Release Profile of the Q3 formulation with marketed formulation

Time	Standard(% Release)	Q3 (% Release)
1	26.33588	22.59542
2	46.10687	39.77099
3	63.05344	56.94656
5	78.0916	72.06107
6	84.12214	77.8626
8	90.30534	95.80153
10	90.40574	95.85175
12	90.60384	95.89166

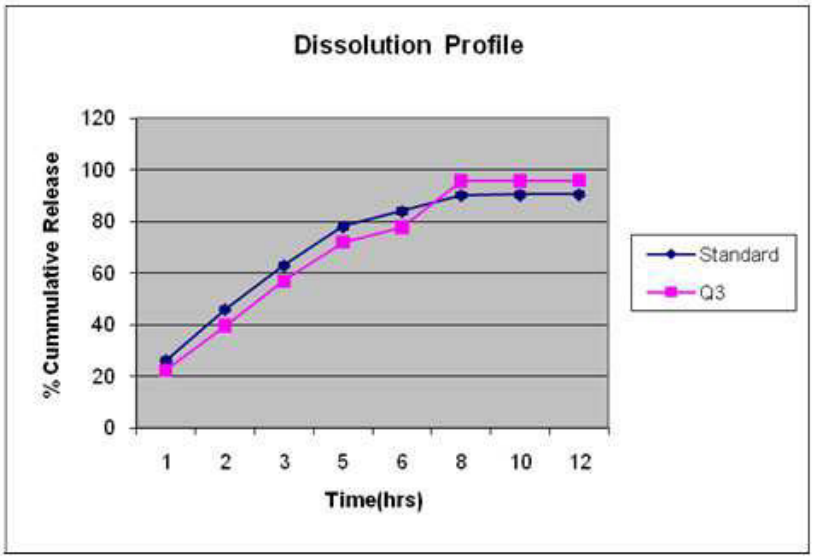

Figure 5
Release Profile of the formulation only with marketed formulation

1.4.2 Surface Characterization (15)

The microcapsules were scanned using scanning electron microscope. The scanning electron micrograph (SEM) of microcapsules showed that microcapsules were spherical in shape with the presence of rough porous polymeric film.

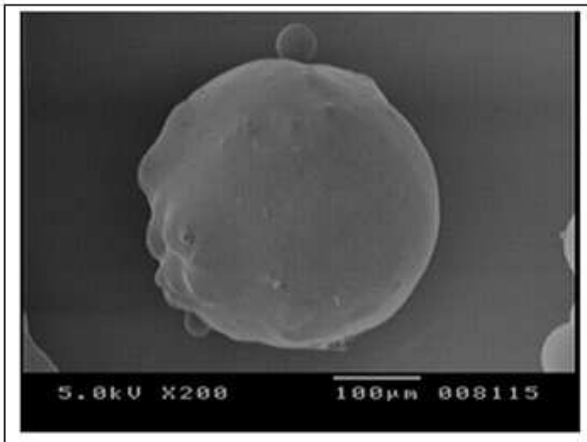

Figure 6: An Intact Microcapsule

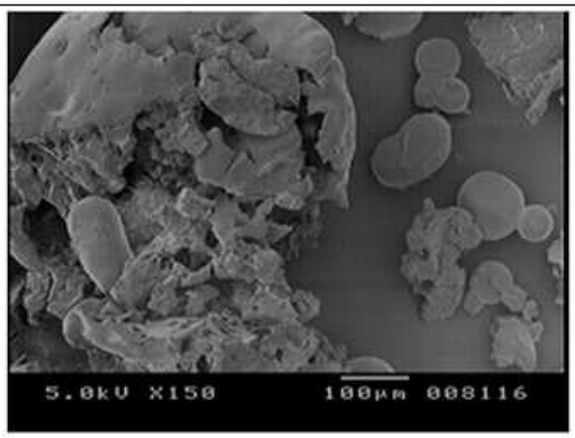

Figure 7: An empty microcapsule after release of drug contents

Compatibility Studies of Q3 (14)

Thermal analysis of the sample was conducted to check for compatibility of Metformin HCl with Ethyl Cellulose and Eudragit® S 100. To characterize the thermal behaviour of microcapsules, Differential Scanning Calorimeter (DSC) analysis was conducted.

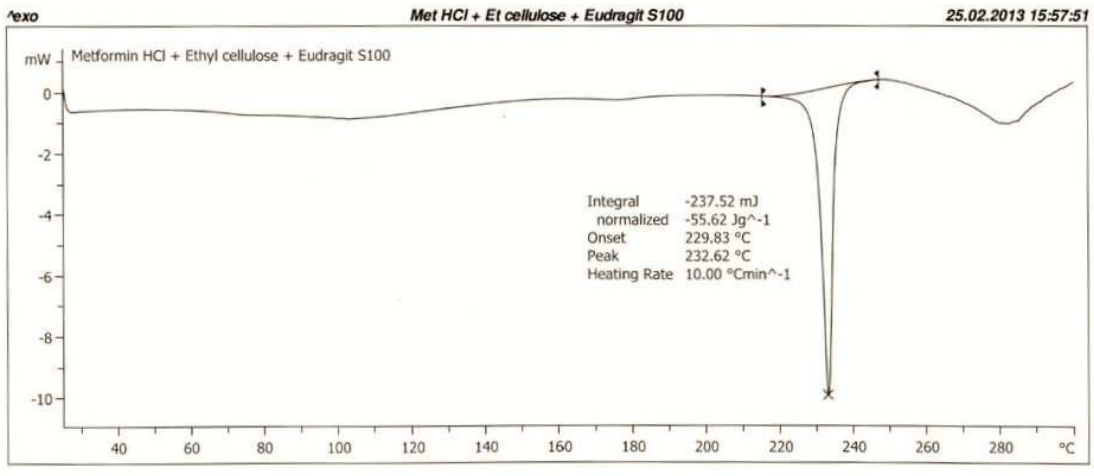

Figure 8
Thermogram of Q3

CONCLUSION

- In present study microcapsules of Metformin HCl were prepared by using different ratios of Drug to Polymer.
- Ethyl Cellulose & Eudragit S 100 in the ratio of 1:1 shows a drug release profile which is comparable to marketed preparation.
- The microspheres prepared by the solvent evaporation method have shown the F2 value 57.
- It also has the advantages of improved palatability and taste masking
- The prepared microspheres would be further optimized using factorial design.
- These microspheres would be further evaluated for its feasibility of conversion into an oral sustained release formulation.
- The suspension will be subjected to stability studies and would be further subjected to IVIVC studies

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