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Ternary complexation approach for the development of oral thin films of Rizatriptan benzoate

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ABSTRACT

The purpose of this research was to formulate fast dissolving oral thin films (OTFs) of the rizatriptan benzoate using ternary complexation approach. Taste masking was done by complexing with beta cyclodextrin and HPMC E5 was not only used as a film forming hydrophilic polymer but also enhances the stability of drug –betacyclodextrin complex which masks the bitterness of drug. Different ratio of drug-betacyclodextrin complex and HPMC E5 concentrations were used in the formulations containing sodium saccharin as sweetening agent and glycerol as plasticizer. The prepared films were evaluated for various parameters like thickness, drug content, surface pH, moisture absorption and moisture loss etc. Tensile strength, folding endurance, in-vitro disintegration time and taste evaluation was also done. Ternary complex formation was confirmed by FTIR and DSC. All the films exhibited good tensile strength and in-vitro disintegration time but formulation $\mathbf{R_6}$ was best formulation in terms of taste, disintegration time and mechanical properties.

Keywords: Oral thin films, fast dissolving, complexation, tastemasking, antimigraine.

INTRODUCTION

Recently OTFs have become an accepted alternative dosage form for pharmaceutical manufacturers to deliver medicines that are usually available as liquids, tablets, or capsules. The benefits of dissolvable oral thin film technology include fast, accurate dosing in a safe and effective manner especially for pediatric and geriatric patients or for patients who have difficulty in swallowing pills or prefer not to do so and for those who suffer from nausea, vomiting leading to noncompliance / unpredictable absorption of drug.[1-2]

Migraine is most common frequently incapacitating headache disorder whose epidemiological studies reveal that large number of patients suffer nausea during the migraine attack (>90%) and most (almost >70%) have vomited during the attack. Thus OTFs will be preferred dosage form for the migraine patients. Triptans are a new class of compounds developed for the treatment of migraine attacks which display high agonist activity at mainly the serotonin 5-HT1B and 5-HT1D receptor subtypes. Rizatriptan Benzoate with its shorter time to maximum concentration (tmax) tended to produce a quicker onset of headache relief than sumatriptan and zolmitriptan. Chemically it is N,Ndimethyl-5-(1H-1,2,4-triazol-1-ylmethyl)-1H-indole-3-ethanamine monobenzoate The initial gut absorption of Rizatriptan is high (90%); however, the compound undergoes moderate first-pass metabolism, which limits the bioavailability to 47% also Its bitter taste is its main drawback [3-4]. It is important to mask unpalatable taste of drug to improve patient compliance. Thus in the present work we have investigated the influence of HPMC E5 and ß cyclodextrin on the formulation of fast dissolving film of rizatriptan benzoate.

HPMC 5 cps is a low viscosity grade hydrophilic polymer and is used extensively in film coating for immediate release solid formulations as well as for fast dissolving oral thin films due to non-ionic character and bland taste.

Use of cyclodextrins as taste masking agent is widely reported due to its ability to form inclusion complexes with various substrates. However their taste masking ability is limited by the fact that the drug which form cyclodextrin complex with low stability constants would lead to a rapid release of free drug in the oral cavity, resulting in inefficient taste masking. Some researchers have masked the taste of rizatriptan benzoate by forming binary complex with ß cyclodextrin. The combination of ß cyclodextrin and HPMC E5 was reported in the literature for the formulating a ternary complex with famotidine by solution method which masked the bitter taste of the drug more effectively than binary complex of drug-ß cyclodextrin.[7,11]

Thus, novelty of work lies in inclusion of ternary complexation ap-

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proach in preparing taste masked fast dissolving film of rizatriptan benzoate.

MATERIAL AND METHOD

Rizatriptan benzoate was supplied by Jubilant life sciences Ltd. (Noida,India), Hydroxy propyl methyl cellulose (HPMC 5 cps)Methocel E5 PREM LV was obtained from Dow Chemicals(Mumbai, India), ß-cyclodextrin purchased from India), glycerol, sodium saccharrin were procured from CDH Laboratories New Delhi. All other chemicals and solvents used were of pharmaceutical and analytical grade. Double distilled water was used throughout the study for experimental work

Preparation of film:

The OTF of rizatriptan(RZB) benzoate was prepared by solvent casting method.[8] An aqueous solution of the cyclodextrin was prepared in distilled water and RZB was dissolved in it. This solution was stirred continuously for 30 minutes, followed by the addition of film former HPMC E5 and stirring was continued to obtain homogenous solution. Glycerol as plasticizer and sodium saccharine were also added in the solution which was sonicated for 30 min to remove entrapped air. The solution was casted on a plastic laminated glass mold and dried at 40-45 C for 24 hr. The film was carefully removed from the mold, checked for any imperfections and cut into the required size. The samples were wrapped in butter paper followed by aluminium foils and stored in a dessicator at relative humidity not more than 40 % until further analysis. Film samples with air bubbles, cuts or imperfections were excluded from the study.

Composition of HPMC E5 based oral films for Rizatriptan benzoate

Ingredients	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	R_9
HPMC(mg)	400	400	400	600	600	600	800	800	800
Rizatriptan Benzoate(mg)	294	294	294	294	294	294	294	294	294
Beta cyclodextrin (mg)	294	441	588	294	441	588	294	441	588
Glycerine(mg)	100	100	100	150	150	150	200	200	200
Saccharine sodium(mg)	1	1	1	1	1	1	1	1	1
Tween 80	0.1	01	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Distilled water (ml)	20	20	20	20	20	20	20	20	20

Evaluation[6-9]

Uniformity of Thickness

The thickness of each OTF formulation (2×2 cm) was measured using a micrometre (Mitutoyo, Japan) at the four corners and centre and the mean value were calculated.

Weight uniformity

For determining the weight uniformity of the films, five different sections of 2X2cm2 film from each batch were cut and weighed individually using electronic balance and standard deviation for each batch was calculated

Drug Content

For determination of drug content 2x2 cm^2 film from each batch was kept in 10 ml phosphate buffer pH 6.8 for 24 h. Then the solution was filtered and drug content was determined using UV spectrophotometer at 225nm. Three readings from each batch were taken. Average and standard deviation for each batch was calculated.

Surface pH study

The surface pH of fast dissolving OTFs was determined to predict the possibility of any discomfort *in vivo*. As an acidic or alkaline pH may cause irritation to the oral mucosa, the surface pH should be as close to neutral as possible. A combined pH electrode was used for this purpose. Oral film was slightly wetted with the help of water. The pH was measured by bringing the electrode in contact with the surface of the oral film. The experiments were performed in triplicate, and average values were reported

Folding Endurance

The OTF (20×20 mm) was repeatedly folded at the same place. The total numbers of folds made before the ?lm cracked were denoted as ?lm ?exibility value/ folding endurance.

Percentage moisture absorption

The percentage moisture absorption test was carried out to check the physical stability of the oral films at high humid conditions. In the present study the moisture absorption capacity of the films were determined as follows. Three 2X2cm^2 films were cut out and weighed accurately then the films were placed in desiccator containing saturated solution of aluminum chloride, keeping the humidity inside the desiccator at 80%. After 3 days the films were removed, weighed and percentage moisture absorption was calculated. Average percentage moisture absorption of three films was found.

$$\text{Percentage moisture absorption} = \frac{\text{final weight} - \text{initial weight}}{\text{Initial weight}} \times 100$$

Percentage moisture loss

Percentage moisture loss was also carried to check the integrity of films at dry condition. Three 2X2cm^2 films was cut out and weighed accurately and kept in desiccator containing fused anhydrous calcium chloride. After 72 hours the films were removed, weighed. Average percentage moisture loss of three films was found out.

$$\text{Percentage moisture loss} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

Tensile Strength Measurement

Mechanical properties of the films (patches) were evaluated using an instrument (Tensile meter, Fibrotech electronics Roorkee), equipped with a 25 kg load cell. Film strip with required dimensions and without any visual defects were cut and positioned between two clams separated by a distance of 3 cm. Clamps were designed to secure the patch without crushing it during the test, the lower clamp was held stationary and the strips were pulled apart by the upper clamp moving at a

rate of 2 mm/sec until the strip broke. The force at the point when the strip broke was recorded. The tensile strength values were calculated using the following formula:

$$Tensile\ strength\ (kg/cm^2) = \frac{Force\ to\ break\ (kg)}{Initial\ cross\ sectional\ area\ of\ the\ sample\ (cm^2)}$$

***In vitro* disintegration studies**:
Disintegration time gives an indication about the disintegration characteristics and dissolution characteristics of the film. The film as per the dimensions (2 x 2 cm) required for dose delivery was placed on a stainless steel wire mesh placed in a petridish containing 10 ml of buffer (pH6.8). The buffer was swirled at every 10 sec and time required for the film to break was observed visually.

In-vitro dissolution studies
The in vitro dissolution studies were conducted using two dissolution media namely, simulated saliva (200 ml). 0.1N HCl (900 ml) and The dissolution studies (n=3) were carried out using USP dissolution apparatus (Electrolab, Mumbai, India) at 37 + 0.5 °C and at 50 rpm using specified dissolution media. Each film with dimension (2 x 2 cm) was placed in a basket and immersed in the specified media. 5 ml of sample were withdrawn at specified time intervals and filtered through Whatman filter paper and were analyzed by spectrophotometer at 225 nm (UV Shimadzu, Japan). The in vitro dissolution profile is shown in Fig.

Fourier Transform Infrared (FT-IR) Studies
Fourier transform infrared (FT-IR) spectra of the samples were obtained in the range of 400 to 4,000 cm-1 using Shimadzu FT-IR spectrophotometer (Japan) by the KBr disc method.

Differential Scanning Calorimetry (DSC) Studies
The samples were subjected to DSC studies using Perkin Elmer, pyris 4 series DSC equipment (Massachusetts, USA). Samples were sealed in 40 µl aluminium pans. An identical empty pan was used as a reference; all samples were scanned at 5 °C/min with a 20 ml/min nitrogen purge.

Taste evaluation.
All the subjects were completely informed concerning the pertinent details and the purpose of the study. A written consent form was supplied, understood, and signed by each subject prior to dispensing the test materials. Films were randomly administered to healthy human volunteers between age group 20–40 years at 2 min time intervals. A specimen of 4 cm^2 was placed in the oral cavity by the volunteer, directly on the tongue. The volunteers were asked to evaluate the film on scale for the bitterness study was as follows:
+ = very bitter,
++ = moderate to bitter,
+++ = slightly bitter,
++++ = tasteless/taste masked

RESULT AND DISCUSSION
Total nine batches of Rizatriptan benzoate loaded fast dissolving oral thin films were formulated; the films were translucent, thin and soft. The films were evaluated in the terms of physico-mechanical properties and the results are given in table II and III.

Table I: Evaluation of oral thin films of rizatriptan benzoate

Formulation	Thickness*	Drug content	Weight* (mg)	Surface pH	PMA	PML
R1	0.112 ± 0.004	94.6±1.04	65.6±0.97	6.97± 0.05	4.12±0.11	5.54±0.23
R2	0.118 ± 0.004	92.5±1.04	74.4±0.73	6.76± 0.08	5.23±0.41	5.97±0.33
R3	0.120 ± 0.004	93.6±0.70	78±0.36	6.81± 0.05	5.74±0.12	6.59±0.54
R4	0.120 ± 0.011	95.4±0.87	71.7±0.26	6.82± 0.05	6.21±0.33	7.32±0.32
R5	0.124 ± 0.004	93.9±0.36	80.5±0.54	6.74± 0.06	6.78±0.43	8.44±0.65
R6	0.128 ± 0.004	93.7±1.00	86.9±0.68	6.90± 0.04	4.56±0.54	4.12±0.21
R7	0.119 ± 0.014	94.6±0.70	85.7±0.55	6.82± 0.03	6.30±0.41	7.34±0.65
R8	0.123± 0.004	94.4±0.30	93.4±0.65	6.93± 0.03	6.51±0.44	6.63±0.32
R9	0.125± 0.004	95.6±0.70	107.4±0.4	6.90± 0.02	6.02±0.35	7.07±0.45

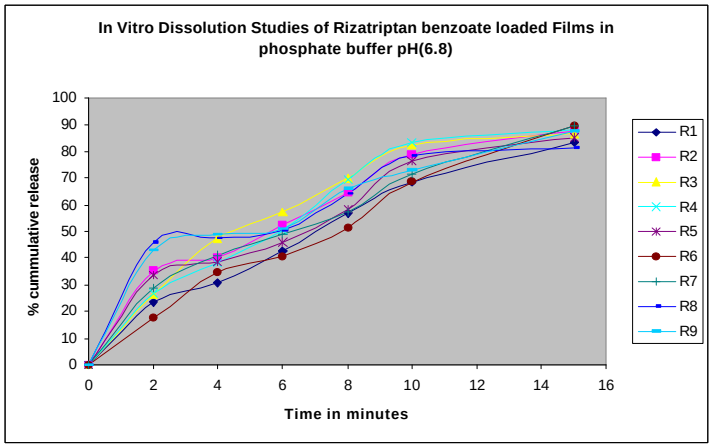
TableII: Result of mechanical properties and disintegration time of oral films

Formulation	Folding endurance	Tensile strength N/cm^2	Disintegration time(sec)	Taste Evaluation
R1	66 ± 2	2.057±0.112	55 ± 1.73	+
R2	59 ± 5	1.584±0.143	59 ± 2	++
R3	50 ± 1	1.031± 0.072	63.66 ± 1.08	++
R4	54 ± 3	2.875± 0.110	60.66 ± 1.1	++
R5	47± 4	2.381± 0.131	65 ± 1.73	++
R6	38 ± 3	2.180±0.048	72.33 ± 1.53	+++
R7	40 ± 2	3.093±0.066	75 ± 2.08	++
R8	43 ± 2	2.639±0.070	78 ± 1.52	+++
R9	39± 3	2.512±0.102	82 ± 1.81	++++

All the films were found to contain an almost uniform quantity of the drug, as per content uniformity studies indicating reproducibility of the technique. Drug content in the films was evaluated and the values were found to be between 92.5% and 95.6%. The surface pH of all the films was found to be 6.5 - 7, which is very similar to pH within oral cavity and thus formulation should not cause any discomfort or irritation. The presence of beta cyclodextrin at higher proportion and increased conc of HPMC lead to films with rough surfaces due to limited solubility of betacyclodextrin also total solid content of the film increases leading to more numbers of pores and microcracks in films resulting in more moisture absorption as well as loss.

Film flexability was found to decrease with increase in ratio of cyclodextrin w.r.t to drug from 1:1 to 1:2 (D: ß cyclodextrin). It also decreases with higher amount of HPMC E5. All the batches of fast dissolving strips for each formulation were found disintegrate in less than 80 sec .*In vitro* disintegration time was found to increase with increase in the amount of HPMC E5 used in the formulations. Films of formulae R1 to R9 were evaluated for Taste on healthy human volunteers. The results of the in-vivo study are shown in TableII. With increase in the concentration of ß cyclodextrin in the formulations the taste was improved. This may be due to ternary inclusion complex formed by triptans with cyclodextrin and HPMC E5. The presence of HPMC E5 enhance the complex stability, also higher the concentration of HPMC E5 , higher is the viscosity and lesser amount of drug diffusion occurs , leading to reduced perception of bitterness.

The *in vitro* drug release profile from the films of formulae R1 to R9 in phosphate buffer pH 6.8 and 0.1 N HCl is shown in Figure and fig respectively. Drug release rate was decreased with higher amount of HPMC E5 in formulation. After 10 minutes time interval more than 60% drug was released from batches at pH 6.8 while more than 90% of the drug was released after 10 min interval from all the films in dissolution media of 0.1 N HCl. The difference in the amount of drug released in different media may be due to the formation of ternary complex from which drug is release more rapidly at the acidic pH than at pH 6.8. These results also support that the film formulation also masked the taste of rizatriptan benzoate in oral cavity.



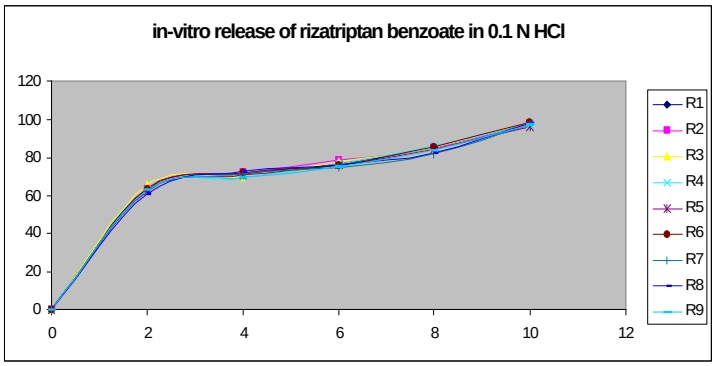


Fig 1: *In vitro* release of rizatriptan benzoate from oral thin films a) salivary pH 6.8 and in 0.1 N HCl.

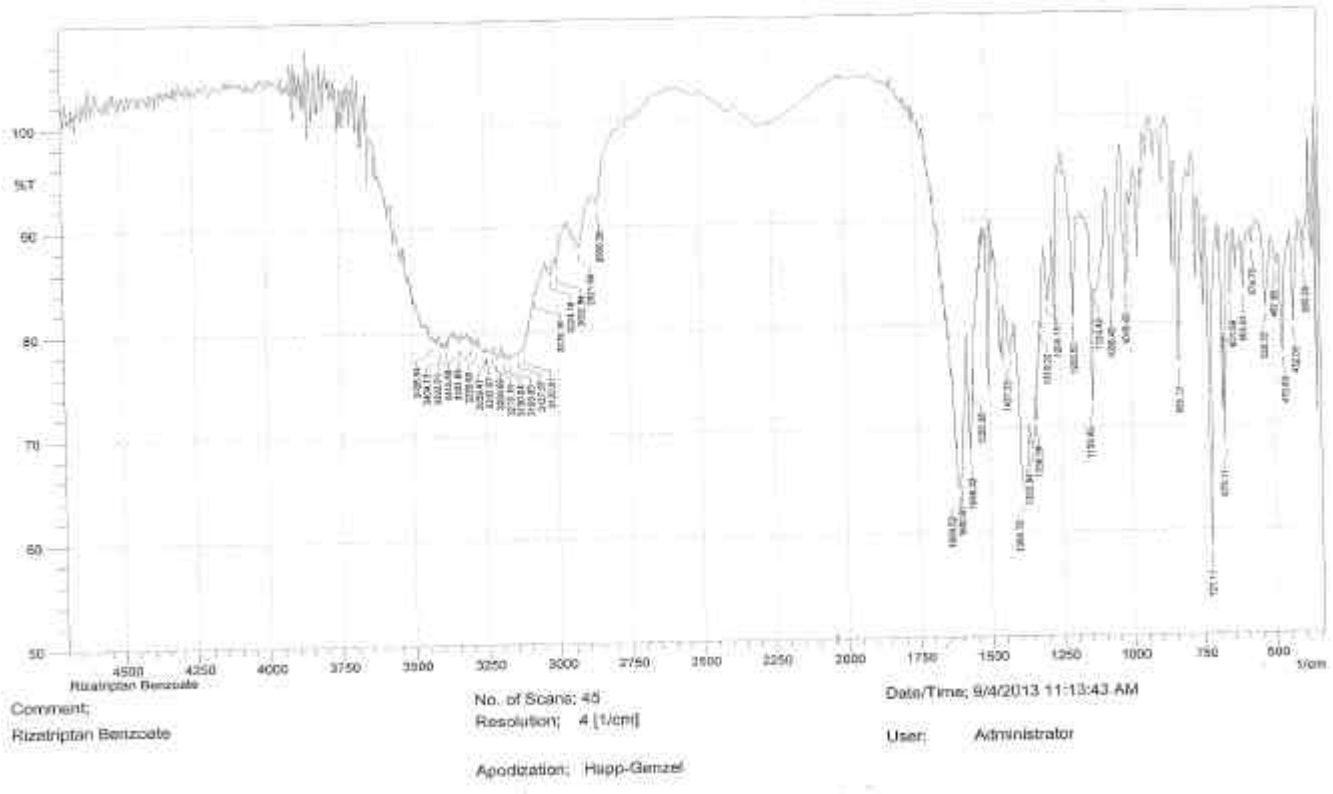
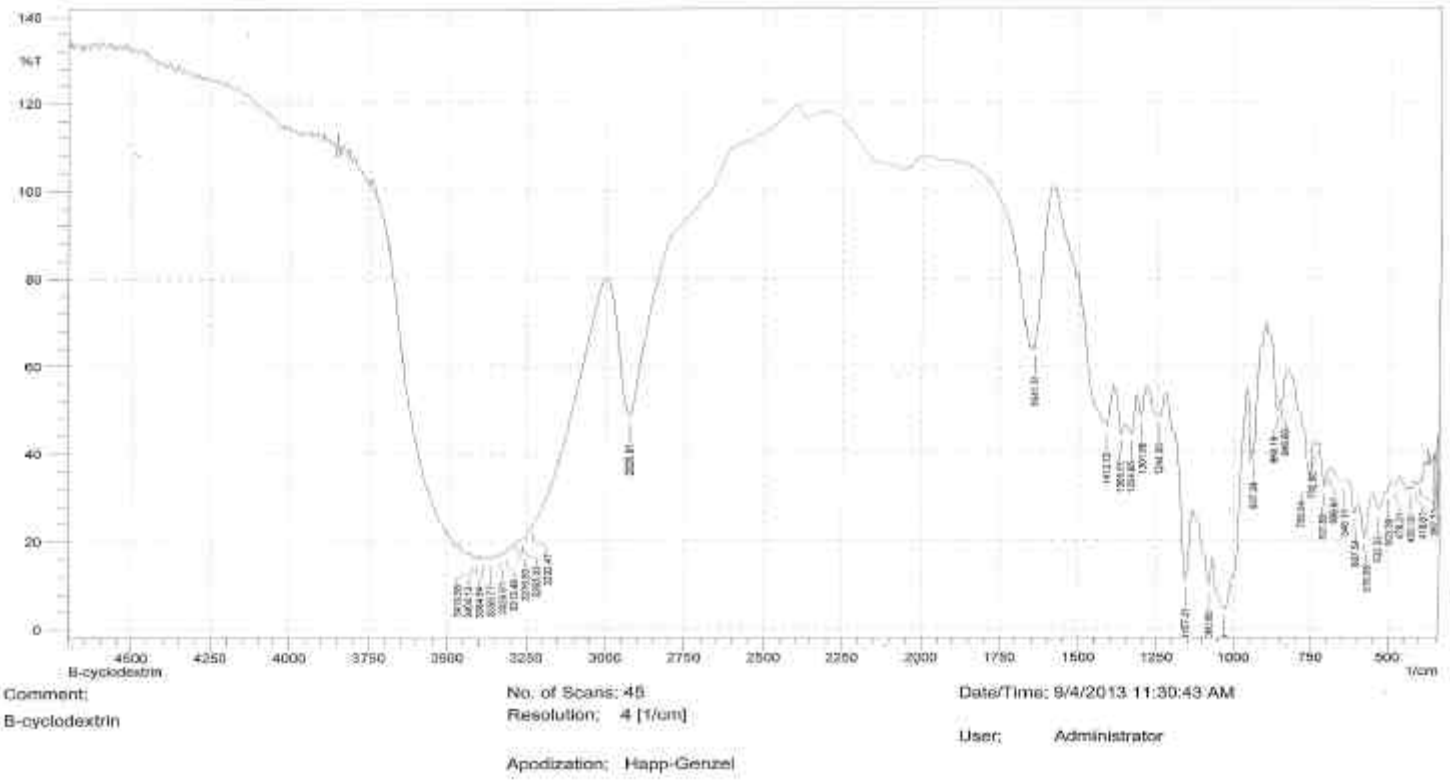
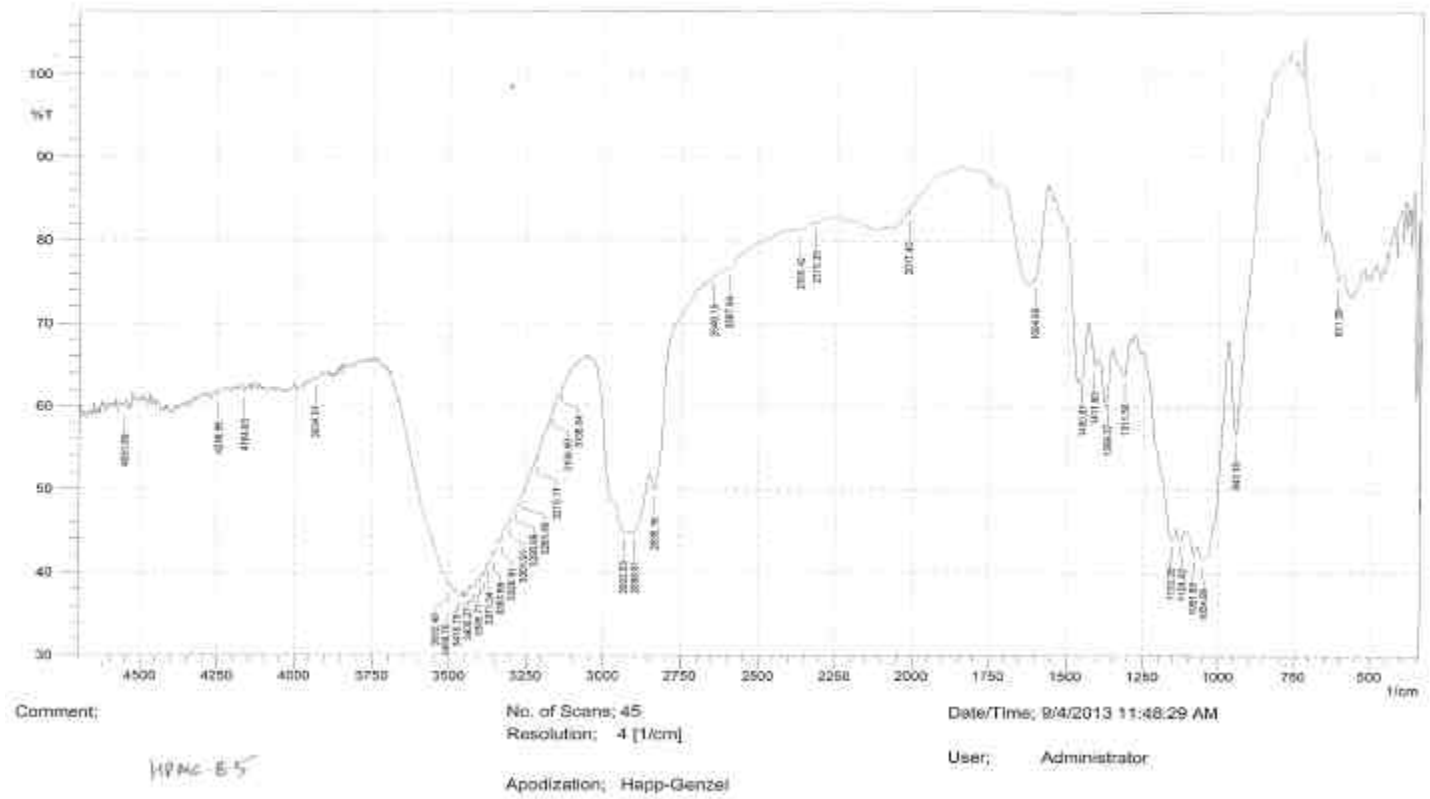


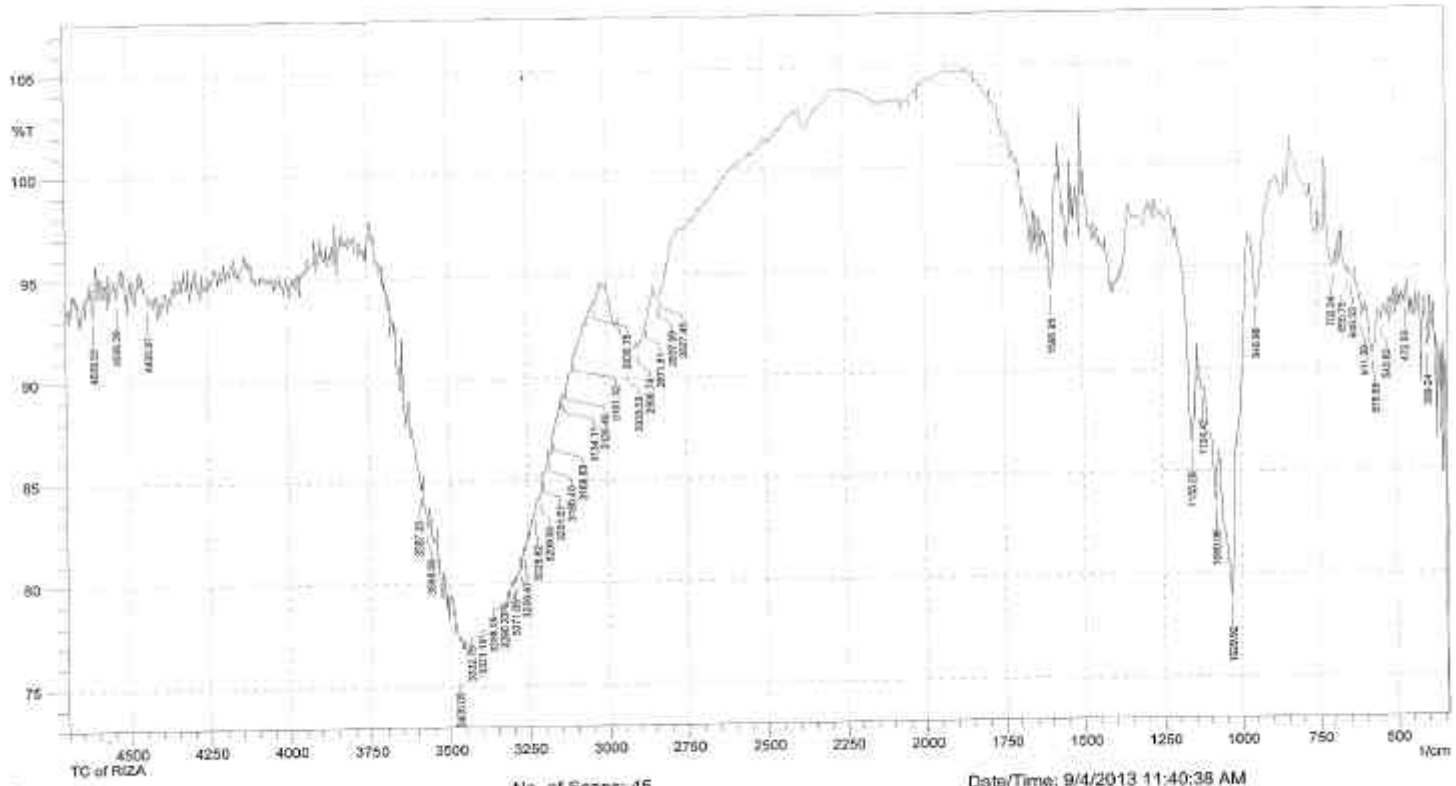
Fig2 :IR of a)Pure drug Rizatriptan benzoate



β-cyclodextrin



HPMC e5



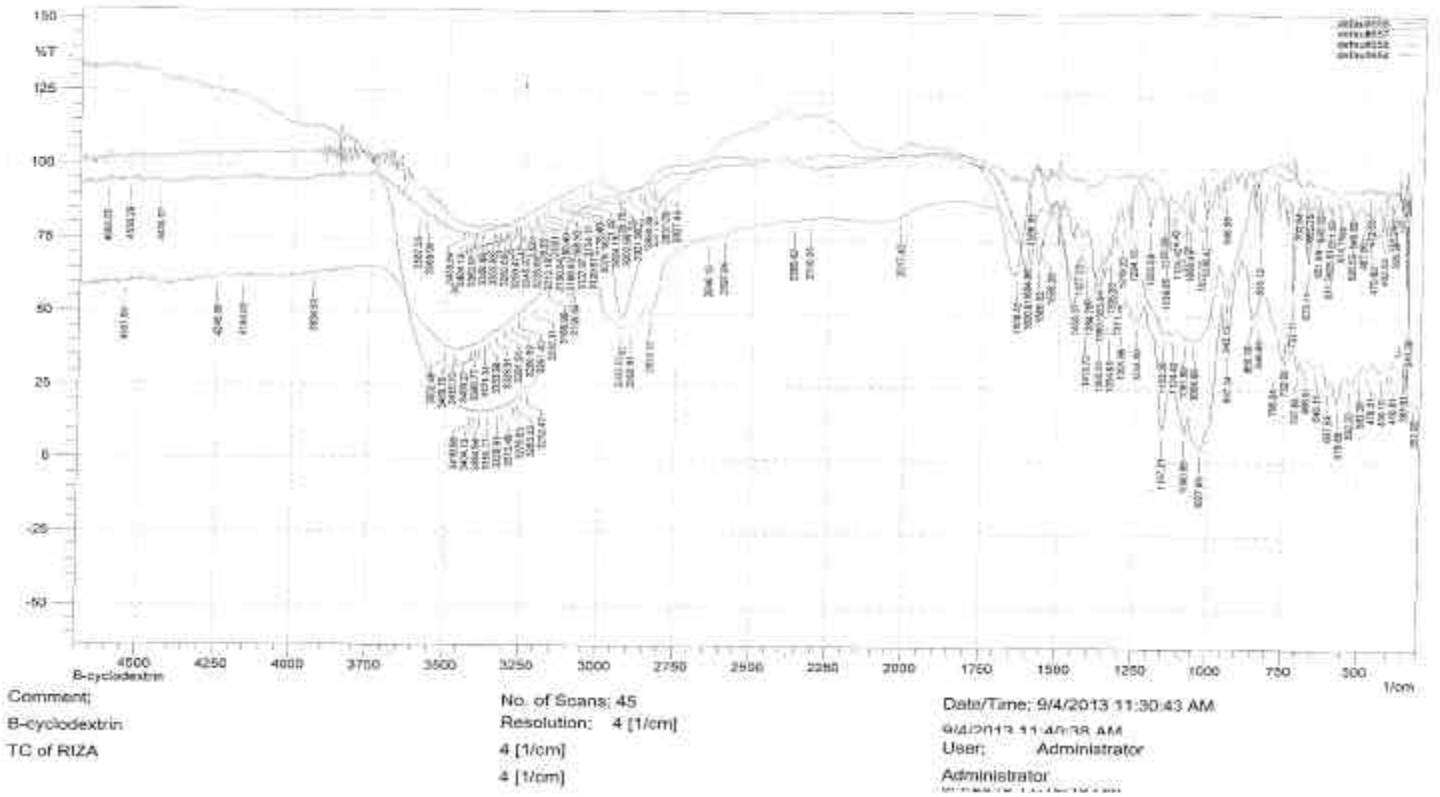


Fig2 :IR of a)Pure drug b)Physical Mixture c) Film

FTIR spectra of the given samples illustrated in figure 2 show that there were no major changes in the FTIR spectra indicating no chemical interaction between the components. Whereas from minor changes in FTIR spectra of film confirm that there is complexation. The pure rizatriptan benzoate exhibited characteristic peaks at 3120 cm^{-1} (aromatic secondary amine N-H stretching), 2912 cm^{-1} (aromatic C-H stretching), 1606 cm^{-1} (C=O five member cyclic stretching) and 1270 cm^{-1} (C-N aliphatic amine stretching).

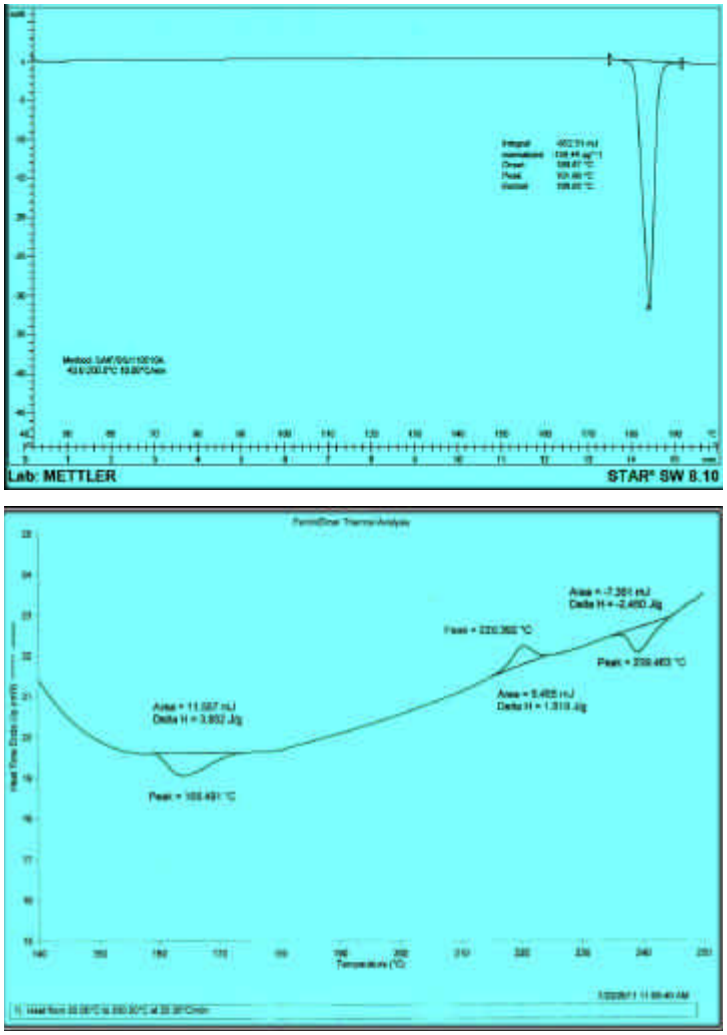


Fig 3 DSC of a) pure rizatriptan benzoate b) ternary complex (drug: beta cyclodextrin : HPMC) 1:1:2

Differential Scanning Calorimentry

Any possible drug polymer interaction can be studied by thermal analysis. Rizatriptan Benzoate exhibits a sharp endothermic peak at 181.99°C shown in Figure 3, which corresponds to its melting point. The shift in the peak of rizatriptan benzoate to 168.49 and its reduced area was may be due to the formation of ternary complex drug with betacyclodextrin and HPMC E5.

CONCLUSION:

The investigation here confirmed that the ternary complexation approach which has been well reported in literature for improving the complexation efficiency of ß-cyclodextrin by increasing the stability can be applied for the successful formulation of fast dissolving oral thin films of bitter drugs like rizatriptan benzoate.

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