DESIGN & ASSESSMENT OF ORAL FILM OF TELMESARTAN FOR TREATMENT OF HYPERTENSION BY USING FIVE DIFFERENT POLYMERS.

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Abstract:

Background: oral dissolving film is a type of drug delivery system where films are dissolved in oral cavity within few seconds and absorbed to produce better therapeutic response. This oral film gaining popularity due to its patient compliance & quick onset of action

Objectives: To design & evaluate the various characteristics of Telmesartan film by using five different polymers for better effect of drug.

Methods and materials: The film was prepared by solvent casting method by using HPMC E5, HPMC E15, Pectin, PVP K-30, sodium alginate as polymer. Glycerol, Polyethylene glycol 400 used as plasticizer & sodium starch glycolate used as disintegrating agent in the formulation. There were 21 formulation prepared & it was analyzed for disintegration time, drug release, weight variation, folding endurance and thickness. The FTIR method was adopted for compatibility study.

Result: The result shows that disintegration time was between 1 to 3 minutes, folding endurance was > 120,optimized formulation shows >90% drug release within 12 minutes and FTIR data shows no interaction between drug and excipients.

Conclusion: The research work shows a good oral film of Telmesartan was prepared by using optimized polymer, KOH as alkalizer for improving solubility & PEG 400 as plasticizer. The results were acceptable for oral film and hence Telmesartan can be formulated as oral film for better therapeutics.

Key words: Telmesartan, Oral dissolving film, solvent casting method,

INTRODUCTION:

Oral route consider as most popular route of administration because of its enormous advantages. The dosage form like tablet, capsule, liquids, and films is administered by oral route. but the oral film place a separate role for oral route due to its easy disintegration in oral cavity, improved bioavailability, avoid of first pass metabolism and patient compliance [1,2].The main component of oral film is polymer, hence selection of polymer play a crucial role for cast of film. Very common polymers that are use in film production are different grades of HPMC (hydroxypropyl methyl cellulose), chitosan, pectin, CMC (carboxy methyl cellulose), PVP (polyvinyl pyrolidine) etc. These polymers may use single or combined of them [3,8]. Highly vascularized oral mucosa permeating many drug & drug directly enter into blood to produce quick onset of action [4]. As the solid dosage form like tablet, capsule is difficult to swallow for pediatric, geriatric patient it is more convenient to use of oral dissolving film. After administration the presence of hydrophilic polymer contact with oral content & dissolve the film inside oral cavity and drug absorbed directly. Many research also revealed that vitamins can be dispensed by oral dispersible film [5,20]. Research and development in the oral drug delivery segment has been led to transition of dosage forms from simple conventional tablets/capsules to oral disintegration tablet (ODT) to wafer to the recent development of oral disintegrating films (ODF) can be considered as an ultra thin strip of postage stamp size with an active agent or active pharmaceutical ingredient and other pharmaceutical excipients. The advantage of convenience of dosing probability of ODF has led to wider acceptability of this dosage form by pediatric as well as geriatric population equally.

Telmesartan (TLM) is an antihypertensive agent cause inhibition of the action of angiotensin II on vascular smooth muscle in the symptomatic treatment of hypertension. The major drawback of this drug is its low aqueous solubility. It is insoluble in water and hence the drug may be slowly or incompletely dissolved in the gastro intestinal tract. The bioavailability of TLM is poor about 45%, which is due to extensive first pass hepatic metabolism [6,19]. The market formulation available for Telmesartan is IR (Immediate release) tablet. The quick onset of action is not achieved with the conventional tablet. Hence rapidly dissolving dosage form, particularly the dosage form that dissolves quickly in saliva and can be administered without need of water. [7]. Hence oral dissolving film of Telmesartan was prepared to produce rapid onset of action.

Special feature of oral dissolving film:[21]

1. Thin elegant film
2. Available in various size and shape
3. Unobstructed
4. Excellent mucoadhesion

5. Fast disintegration
6. Rapid release

MATERIALS & METHODS:

Materials:

The chemicals used in this research work were Telmesartan(API) HPMC E5,HPMC E15, pectin, PVP K-30,sodium alginate, carboxy methyl cellulose, glycerol, Sodium starch glycolate, PEG 400, potassium hydroxide, citric acid, sodium saccharin.

Methods:

Screening of the components for formulation of placebo fast dissolving films:

HPMC is known for its good film forming properties and has excellent acceptability. Hence, various grades of HPMC namely, Methocel E5 and Methocel E15 were evaluated as film formers. For the fabrication of films, glycerin was used as humectants. Apart from these film formers, polyvinyl pyrrolidone k-30, sodium alginate, pectin,CMC, alone or in combination with plasticizers were tried. The composition of various placebo films is given in Table 1. The films were prepared by solvent casting method. The polymer was soaked in water for 30 min or heated in water bath to 80º to get a clear solution. Then a plasticizer was added to it and mixed so as to get homogeneous solution. This solution was then casted onto a glass petridish (8.4 mm in diameter) and was dried in hot air oven at 45° for 24 h. The films were evaluated for imperfections, peelability without rupturing, surface roughness, appearance and in vitro disintegration time . Optimization was further performed for the polymer and plasticizer compositions which showed good film properties.

Table 1: composition of placebo trials.

Table 2: Evaluation of placebo film trials

Figure 1: different types of placebo film

After observing the above parameter of placebo film, the research was forward for optimization of composition by using selected polymer & plasticizer (PEG 400 & propylene glycol). The composition of formulation was given in table 3.

Table 3: composition of formulation with selected polymer obtained from placebo trial

All the formulation (F1-F18) were analyzed for appearance, film forming capacity, folding endurance & disintegration time for further optimization. The observations are presented in table 4.

Table 4: Analysis of various physical parameters for formulation F1-F18

Evaluation of Telmesartan oral film:

Film thickness determination: After preparation of film, the thickness has to be determined by using screw gauge. While measured all four sides & centre must be include as part of measurement. Four samples of each batch was selected for measurement [9,10]

Determination of film weight: weight variation test was done by using electronic balance to find out whether all the films are uniform or not. For that 2x2 cm2 film was cut and weight is measured. Six films from each batch was calculated [11]

Drug content: The selected size of film was dissolved in phosphate buffer pH 6.8 then filters it. The filtrate used with suitable dilution to measure absorbance at 294 nm by using UV visible spectrophotometer. All the determination done in triplicate to get average value [12]

Determination of folding endurance:
The 2 cm x 2 cm film was repeatedly folded at the same place until the film cracked. The number of times the film was folded was denoted as the fold endurance value. The experiment was performed in triplicates and average value was determined [13, 14]

Determination of disintegration time: Petri dish was selected for this test. The water (10 ml) was put inside the petridish containing film. It is necessary to swirl the water every 10 sec to facilitate the process. The time at which film start to disintegrate note down. The process repeated 3 times to get the average value.[15]

Determination of percentage Moisture loss: Film of 2 cm x 2 cm size was selected. Initially weight of film was recorded then it was put inside the desiccator containing saturated solution of K_2SO_4 .At specific time interval film weight was measured till get constant weight of film [16]. The moisture content was determined by using following formula.

Percentage moisture loss = (Initial weight - final weight) / (Initial weight) × 100

In-vitro drug release study: for this study a dissolution apparatus II (paddle type) was used. The phosphate buffer of pH 6.8 was used as dissolution medium. The dissolution medium was maintained at 37±0.5^{o}C with paddle rotation speed at 50 rpm. The volume of medium was 300 ml. At specific time interval sample was drawn & analyzed with UV VIS spectrophotometer [17].

FTIR analysis: The study was conducted to determine the compatibility of drug & excipients. The FTIR spectra were recorded for pure Telmesartan pure drug & formulation. The sample was scanned over 4000-400 cm-1 [18].

Results & Discussion:

Preparation of drug loaded film:

Based on screening of polymer & plasticizer the final formulations batch was prepared. The formulation contain drug, polymer, plastisizer, superdisintegrating agent (sodium starch glycolate), KOH (Solubilizing agent), sodium saccharin (sweetening agent). The amount of Telmesartan in the formulation was calculated based on size of film required & area of petridish used to cast film. After selecting plasticizer the final formulation table was prepared. The final formulation table was presented in table no 5.

Table 5: formulation table of prepared oral film

FTIR study: from the FTIR study it was found that there was no interaction among the drug & excipients. The spectra were presented in figure 2.

DSC study: A DSC study was conducted for pure drug (Telmesartan), placebo formulation (without API) and formulation (containing API) by using Shimadzu,DSC-60 Japan. The temperature range was used as 20-300^{o}C. The Thermogram was presented in figure -3.

Evaluation of oral film loaded with Telmesartan: After preparation of various formulations by using 3- different concentration of polymer, their physical properties analyzed. it was presented on table no 6.

Table 6: Study of different parameter of prepared oral film

Formulation	Thickness (mm)	Folding endurance	Invitro disintegration time (seconds)	Weight variation (mg)	Drug content (%)
FF1	0.34±0.4	41±057	176	0.975±0.006	87
FF2	0.38±0.6	45±0.5	124	0.985±0.04	84
FF3	0.37±0. 1	43±0.8	230	0.986 ±0.01	89
FF4	0.54±0.7	52±0.81	189	0.983±0.002	81
FF5	0.5±0.6	54±0.57	113	0.981±0.004	83
FF6	0.5±0.1	65±0.57	122	0.989±0.004	87
FF7	0.57±0.5	95±0.8	79	0.978±0.02	92
FF8	0.59±0.2	87±0.4	97	0.979±0.03	89
FF9	0.52±0.1	73±0.2	99	0.983±0.001	91

From the analysis it was found that weight variation range from 0.975±0.006 to 0.986 ±0.01,folding endurance was from 41±057 to 95±0.8, in-vitro disintegration time(seconds) from 79 to 230 and drug content vary from 83% to 91%.

In-vitro release study: The in-vitro release was conducted by using USP apparatus II. The phosphate buffer having pH 6.8 was used as dissolution medium with stirring speed 50 rpm. The results were presented in table no 7

Table 7: In-vitro release study of different oral film

Time (min)	FF1	FF2	FF3	FF4	FF5	FF6	FF7	FF8	FF9
0	0	0	0	0	0	0	0	0	0
2	21.19±0.12	21.41±0.44	14.58±0.42	17.59±0.42	15.59±0.42	11.97±0.42	32.21±0.35	22.21±0.35	17.21±0.25
4	31.67±0.35	32.49±0.22	24.13±0.32	28.68±0.43	25.79±0.44	21.52±0.44	61.45±0.42	31.45±0.42	26.45±0.22
6	48.19±0.42	43.29±0.22	39.86±0.22	39.38±0.46	38.20±0.36	37.91±0.32	84.01±0.28	44.01±0.28	37.01±0.38
7	59.68±0.22	54.77±0.32	52.61±0.42	57.05±0.48	58.55±0.41	47.10±0.23	93.16±0.46	63.16±0.46	46.16±0.26
8	67.16±0.19	62.98±0.48	64.07±0.46	68.82±0.49	61.77±0.35	58.85±0.18	94.21±0.37	71.21±0.37	54.21±0.37
9	78.65±0.26	78.89±0.52	79.26±0.43	79.31±0.23	73.86±0.32	66.16±0.29	96.08±0.39	82.08±0.39	63.08±0.39
10	84.13±0.22	83.21±0.22	81.21±0.44	84.32±0.28	84.23±0.23	72.32±0.32	99.01±0.42	88.01±0.12	72.01±0.32
11	89.21±0.42	88.37±0.28	88.23±0.22	91.21±0.45	88.32±0.41	84.21±0.44	-	94.23±0.07	81.02±0.22
12	92.65±0.41	92.38±0.52	91.68±0.32	93.21±0.39	89.32±0.42	89.65±0.39	-	97.28±0.28	89.23±0.28
13	95.68±0.32	94.65±0.37	93.93±0.52	94.25±0.41	93.21±0.46	91.32±0.17	-	99.26±0.32	92.28±0.32
14	99.23±0.27	96.24±0.38	94.23±0.28	96.32±0.47	94.23±0.43	94.26±0.41	-	-	95.32±0.29
15	-	97.24±0.52	95.01±0.37	99.21±0.36	96.32±0.27	95.28±0.44	-	-	98.83±0.31

From the above table it was observe that the percentage drug release faster in case of pectin based gel i.e. it can be inference that with increasing polymer concentration the release rate was retarded due to more viscosity of formulation and drug molecule required more time to pass through the polymeric membrane. The formulation FF7 (contain pectin 300 mg) shows release of

drug 99.01±0.42 in 10 minutes which was faster as compare with other. Hence formulation FF7 was considered as optimized formulation of the research work.

FTIR study: The result obtained from FTIR study indicates no interaction among the formulation ingredients. Hence all ingredients of formulation are suitable for formulation design.The spectra shown in figure 2.

Conclusion: The Research work of Telmesartan shows it's suitability to formulate into oral film & hence drug can formulate in film form to produce quick & effective therapeutic response. Among all the formulation, the FF7 shows best formulation characteristics; hence it is choose as optimized formulation for Telmesartan to prepare oral film.

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Table 1: composition of placebo trials.

Ing (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16	F17	F18	F19	F20	F21
HPMC E5	300	400	500																		
HPMC E15				300	400	500															
PECTIN							300	400	500												
PVP K30										200	300	400									
Sodium alginate													300	350	400						
CMC																150	200	250	300	350	400
Glycerol(ml)	1	1	1	1	1	1	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
SSG	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2

Table 2: Evaluation of placebo film trials

Ingredients name	Appearance	Film forming properties	Folding endurance	Disintegration
Hpmc E5	Transparent	Very good	75-85	6-8 min
Hpmc E15	Semi transparent	Very good	50-60	8-12min
Pectin	Transparent	Excellent	100-150	1-2 min
PVP K30	Semi-transparent (Not peelable)	Not good	Not conducted (due to non-peelable)	Not conducted (due to non-peelable)
Sodium alginate	Semi-transparent (Not peelable)	Not good	Not conducted (due to non-peelable)	Not conducted (due to non-peelable)
CMC (carboxy methyl cellulose)	Semi-transparent (Not peelable)	Sticky in nature	Not conducted (due to non-peelable)	Not conducted (due to non-peelable)

Table 3: composition of formulation with selected polymer obtained from placebo trial

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16	F17	F18
HPMC E5	300	400	500	300	400	500												
HPMC E15							300	400	500	300	400	500						
pectin													300	400	500	300	400	500
Propylene glycol (ml)	0.25	0.5	0.75				0.25	0.5	0.75				0.25	0.5	0.75			
Polyethylene glycol 400 (ml)				0.25	0.5	0.75				0.25	0.5	0.75				0.25	0.5	0.75

Table 4: Analysis of various physical parameters for formulation F1-F18

Formulations	Appearance	Film forming	Folding endurance	Disintegration
F1	Transparent	excellent	121	7min
F2	Transparent	Very good	46	4min
F3	Transparent	Very good	40	7min
F4	Transparent	excellent	210	7min
F5	Transparent	excellent	130	7min
F6	Transparent	excellent	150	6min
F7	Semi transparent	Good	90	2min
F8	Semi transparent	Good	120	4min
F9	Semi transparent	Very good	101	2min
F10	Semi transparent	excellent	130	3min
F11	Semi transparent	excellent	150	2min
F12	Semi transparent	Good	120	4min
F13	Transparent	Very good	60	2min
F14	Transparent	Very good	100	3min
F15	Transparent	Very good	90	3min
F16	Transparent	Excellent	120	2min
F17	Transparent	Very good	130	3min
F18	Transparent	Very good	110	3min

Table 5: formulation table of prepared oral film

Ingredients	FF1	FF2	FF3	FF4	FF5	FF6	FF7	FF8	FF9
Telmisartan (API)	251mg	251mg	251mg	251mg	251mg	251mg	251mg	251mg	251mg
HPMC E15	300mg	400mg	500mg	-	-	-	-	-	-
HPMC E5	-	-	-	300mg	400mg	500mg	-	-	-
PECTIN	-	-	-	-	-	-	300mg	400mg	500mg
PEG 400	1ml	1ml	1ml	1ml	1ml	1ml	1ml	1ml	1ml
Citric acid	10mg	10mg	10mg	10mg	10mg	10mg	10mg	10mg	10mg
SSG	2mg	2mg	2mg	2mg	2mg	2mg	2mg	2mg	2mg
KOH	50mg	50mg	50mg	50mg	50mg	50mg	50mg	50mg	50mg
Sodium saccharine	10mg	10mg	10mg	10mg	10mg	10mg	10mg	10mg	10mg
Distilled water	10ml	10ml	10ml	10ml	10ml	10ml	10ml	10ml	10ml

Table 6: Study of different parameter of prepared oral film

Formulation	Thickness (mm)	Folding endurance	Invitro disintegration time (seconds)	Weight variation (mg)	Drug content (%)
FF1	0.34±0.4	41±057	176	0.975±0.006	87
FF2	0.38±0.6	45±0.5	124	0.985±0.04	84
FF3	0.37±0. 1	43±0.8	230	0.986 ±0.01	89
FF4	0.54±0.7	52±0.81	189	0.983±0.002	81
FF5	0.5±0.6	54±0.57	113	0.981±0.004	83
FF6	0.5±0.1	65±0.57	122	0.989±0.004	87
FF7	0.57±0.5	95±0.8	79	0.978±0.02	92
FF8	0.59±0.2	87±0.4	97	0.979±0.03	89
FF9	0.52±0.1	73±0.2	99	0.983±0.001	91

Table 7: In-vitro release study of different oral film

Time (min)	FF1	FF2	FF3	FF4	FF5	FF6	FF7	FF8	FF9
0	0	0	0	0	0	0	0	0	0
2	21.19±0.12	21.41±0.44	14.58±0.42	17.59±0.42	15.59±0.42	11.97±0.42	32.21±0.35	22.21±0.35	17.21±0.25
4	31.67±0.35	32.49±0.22	24.13±0.32	28.68±0.43	25.79±0.44	21.52±0.44	61.45±0.42	31.45±0.42	26.45±0.22
6	48.19±0.42	43.29±0.22	39.86±0.22	39.38±0.46	38.20±0.36	37.91±0.32	84.01±0.28	44.01±0.28	37.01±0.38
7	59.68±0.22	54.77±0.32	52.61±0.42	57.05±0.48	58.55±0.41	47.10±0.23	93.16±0.46	63.16±0.46	46.16±0.26
8	67.16±0.19	62.98±0.48	64.07±0.46	68.82±0.49	61.77±0.35	58.85±0.18	94.21±0.37	71.21±0.37	54.21±0.37
9	78.65±0.26	78.89±0.52	79.26±0.43	79.31±0.23	73.86±0.32	66.16±0.29	96.08±0.39	82.08±0.39	63.08±0.39
10	84.13±0.22	83.21±0.22	81.21±0.44	84.32±0.28	84.23±0.23	72.32±0.32	99.01±0.42	88.01±0.12	72.01±0.32
11	89.21±0.42	88.37±0.28	88.23±0.22	91.21±0.45	88.32±0.41	84.21±0.44	-	94.23±0.07	81.02±0.22
12	92.65±0.41	92.38±0.52	91.68±0.32	93.21±0.39	89.32±0.42	89.65±0.39	-	97.28±0.28	89.23±0.28
13	95.68±0.32	94.65±0.37	93.93±0.52	94.25±0.41	93.21±0.46	91.32±0.17	-	99.26±0.32	92.28±0.32
14	99.23±0.27	96.24±0.38	94.23±0.28	96.32±0.47	94.23±0.43	94.26±0.41	-	-	95.32±0.29
15	-	97.24±0.52	95.01±0.37	99.21±0.36	96.32±0.27	95.28±0.44	-	-	98.83±0.31

Figure 1: different types of placebo film

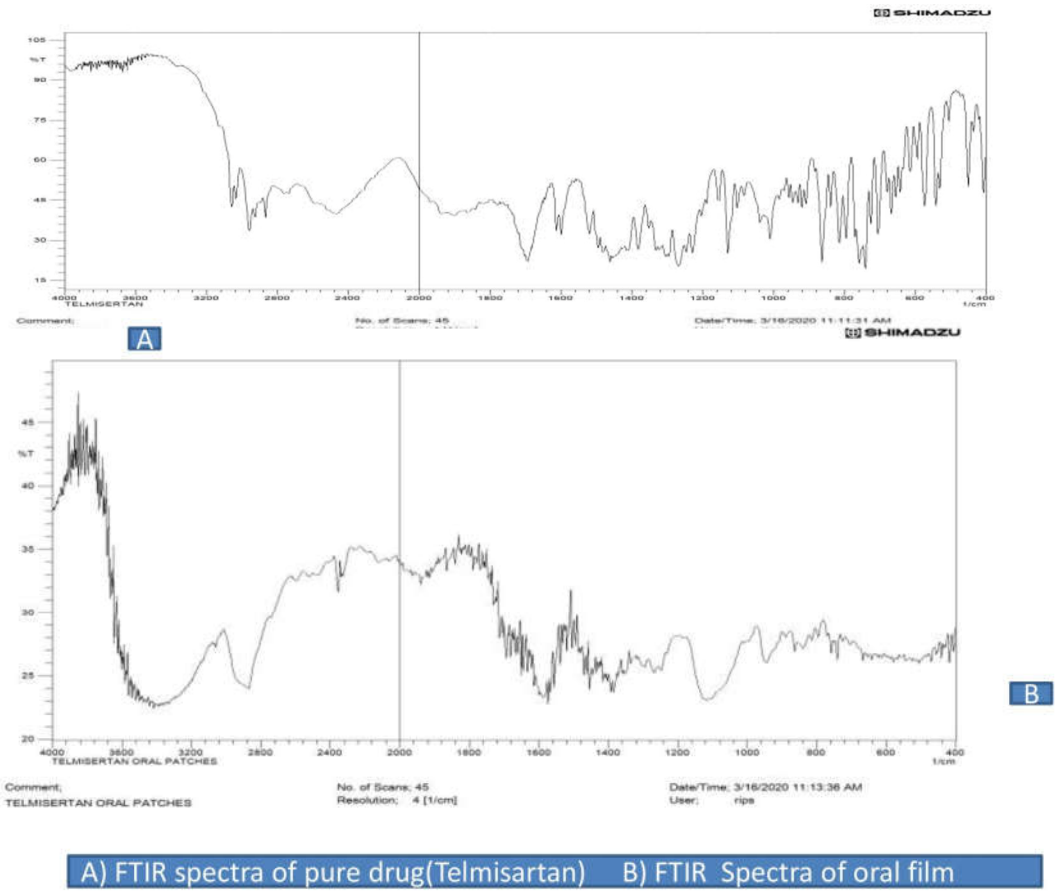

Figure 2: A) FTIR spectra of pure drug B) FTIR spectra of Oral Film

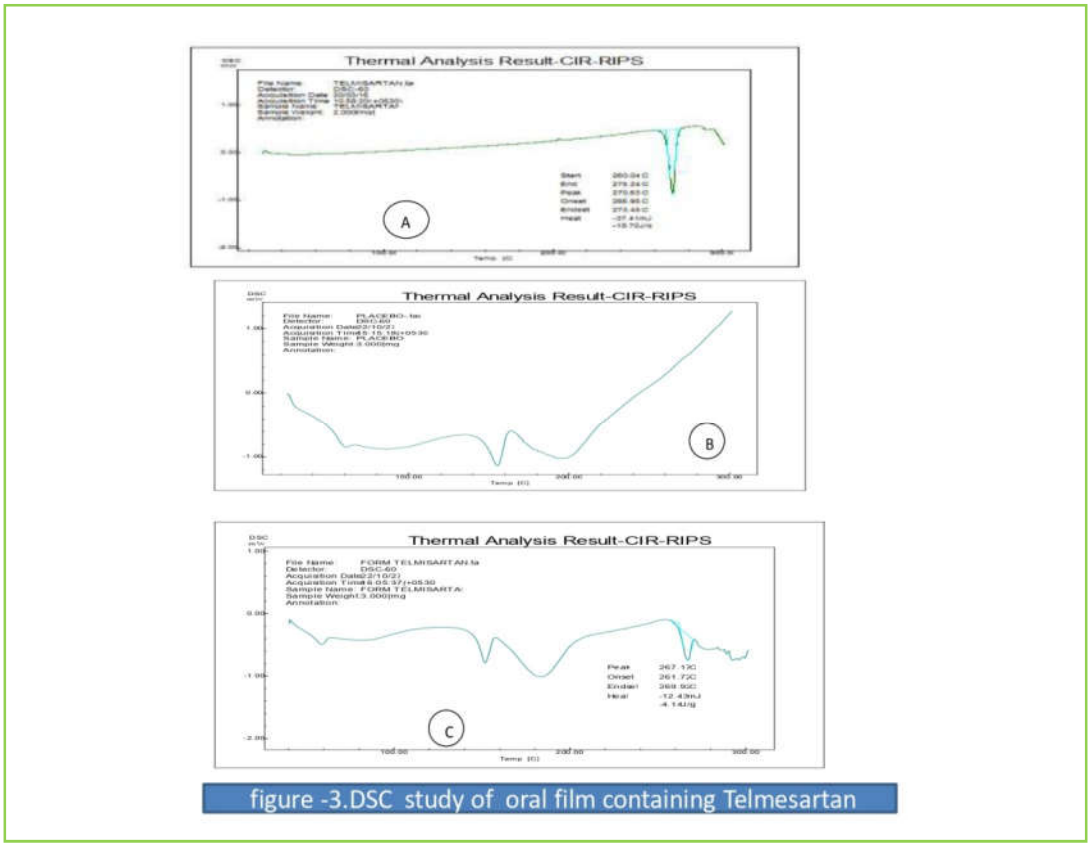

Figure 3: A) DSC of pure drug B) DSC of placebo formulation C) DSC of formulation containing API