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DEVELOPMENT, FORMULATION AND EVALUATION OF SOLIFINACIN SUCCINATE IMMEDIATE RELEASE ORAL TABLETS BY USING STARCH AND HPMC

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ABSTRACT

Overactive bladder (OAB) is a prevalent condition which has an adverse effect on quality of life. The presence of urgency incontinence confers significant morbidity above and beyond that of OAB sufferers who are continent. The primary treatment for OAB and urgency incontinence is a combination of behavioral measures and antimuscarinic drug therapy. The ideal antimuscarinic agent should effectively relieve the symptoms of OAB, with the minimum of side effects; it should be available as a once-daily sustained release formulation and in dosage strength that allows easy dose titration for the majority of sufferers. Solifenacin succinate was launched in 2005 and has been shown in both short and long term clinical trials to fulfill these requirements. Solifenacin is a competitive M3 receptor antagonist with a long half-life (45-68 hours). It is available in two dosage strengths namely a 5 or 10 mg once-daily tablet. The efficacy and tolerability of solifenacin for the treatment of all symptoms of OAB has been evaluated in a number of large, placebo controlled, randomized trials. Long-term safety, efficacy, tolerability and persistence with treatment have been established in an open label 40 week continuation study.

KEYWORDS

Solifenacin, Urinary incontinence, Overactive bladder and Wet granulation method.

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INTRODUCTION

Drug delivery systems (DDS) are a strategic tool for expanding markets/indications, extending product life cycles and generating opportunities. Oral administration is the most popular route for systemic effects due to its ease of ingestion, pain, avoidance, versatility and most importantly, patient compliance. Also solid oral delivery systems do not require sterile conditions and are therefore, less expensive to

manufacture[1]. Patient compliance, high-precision dosing, and manufacturing efficiency make tablets the solid dosage form of choice. Excipients and equipments choices will be significantly affected should solid dosage form technologies change in response to the unprecedented shifts in the drug discovery such as genomics. Should next generation drugs are predominantly protein or peptide based, tablets may no longer be the dominant format give the difficulty of dosing such moiety. Injections generally are not favored for use by patients unless facilitated by sophisticated auto injectors. Inhalation is one good alternative system to deliver these drugs, but the increased research into biopharmaceuticals so far has generate predominantly chemical entities with low molecular weights. The development of enhanced oral protein delivery technology by Fast dissolving Tablets which may release these drugs in the mouth are very promising for the delivery of high molecular weight protein and peptide[2, 3, 4]. The oral route remains the perfect route for the administration of therapeutic agents because the low cost of therapy, manufacturing and ease of administration lead to high levels of patient compliance. Many patients have difficulty swallowing tablets and hard gelatin capsules and consequently do not take medications as prescribed. It is estimated that 50% of the population is affected by this problem, which results in a high incidence of noncompliance and ineffective therapy[5, 6]. The demand for solid dosage forms that can be dissolved and suspended in water, chewed, or rapidly dissolved in the mouth is particularly strong in the pediatric and geriatric markets, with further application to other patients who prefer the convenience of a readily administered dosage form. Because of the increase in the average human life span and the decline with age in swallowing ability, oral tablet administration to patients is a significant problem and has become the object of public attention. The problem can be resolved by the creation of rapidly dispersing or dissolving oral forms, which do not require water to aid swallowing. The Center for Drug Evaluation and Research (CDER), US FDA defined Oral Disintegrating Tablets (ODT) as "A solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue". A fast dissolving tablet can be defined as a solid dosage form that can disintegrates into smaller granules which slowly dissolve in the mouth. The disintegration time for fast dissolving tablet varies from a few seconds to more than a minute depending on the formulation and the size of the tablet.

The dosages forms are placed in the mouth, allowed to disperse or dissolve in the saliva, and then are swallowed in the normal way[7]. Less frequently, they are designed to be absorbed through the Buccal and esophageal mucosa as the saliva passes into the stomach. In the latter case, the bioavailability of a drug from fast dispersing formulations may be even greater than that observed for standard dosage forms.

MATERIALS AND METHODS

MATERIALS

Solifenacin succintate was obtained as a gift sample from Aurobindo pharma ltd. Cross carmellose sodium, Cross povidine, Micro crystalline cellulose, Talc and Titanium dioxide were obtained from SD Fine chemicals, Mumbai. Camphor, Magnesium stearate was obtained from Central drug house ltd, New delhi. All the ingredients used were of analytical grade.

METHODS

Solifenacin, lactose, starch, magnesium stearate and talc through 40# separately. The drug was mixed with proper portion of superdisintegrant. The blended materials were transferred to RMG, then drug solution was added to the blend which acts as a granulating fluid and granulation was carried out by setting the required speed. The wet mass was kept in tray dryer at an inlet temperature of 45±5°C for 60 min. The dried granules were passed through sieve number 22 to get uniform sized granules. Granules were lubricated by adding appropriate quantity of colloidal silicone dioxide and magnesium stearate. The lubricated granules were transferred into the

hopper, and then the compression machine was run to get tablets. Transferred the core tablets into the coating pan, carried out film coating up to desired tablet weight and thickness with dry white by following SOP for film coating.

EVALUATION PARAMETERS

Pre-formulation Studies

Sieve Analysis

The main aim of sieve analysis is to determine the different size of drug particles present. A series of standard sieve are 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).

Procedure

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

Drug - Excipient Compatibility Studies

Compatibility studies are carried out to study the possible interactions between Solifenacin succinate and other inactive ingredients.

Procedure

The compatibility studies are carried out by taking a mixture of drug and excipients at the ratio in which they are expected to be present in the innovator product. A part of mixture can be exposed to different storage conditions like 40±2^{o}C /75% RH ±5% RH and control samples were to be kept at 2-8^{o}C. They are tested with respect to their physical and chemical aspects. These samples are collected at regular intervals and subjected to Differential Scanning Calorimetric analysis.

FT-IR Spectrophotometric Method

It is performed by KBr pellet method. KBr is dried in oven at 45 ^{o}C before analysis. The pure drug is triturated with KBr and pellet is prepared by setting the pressure to 100 kg/cm^2 for 2 minutes. The obtained pellet is analyzed in FTIR 8400 S, Shimadzu, Japan. KBr background was obtained initially before analysis of test samples. The same procedure is repeated for analysis of drug and excipients mixture free from moisture content is used for analysis.

Pre-compression studies

Bulk density

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weight powder (passed through standard sieve #20) into a measuring cylinder and initial weight was noted. This initial volume is called the bulk volume. It is expressed in g/ml and is given by

$$D_b = M / Vb$$

Where,

M is the mass of powder

Vb is the bulk volume of the powder.

Tapped Density

It is the ratio of the total mass powder to the tapped volume of the powder. It was determined by placing a graduated cylinder, containing a known mass of drug-excipients blend. The cylinder was allowed to fall under its own weight onto a hard surface from the height of 10cm at 2 second intervals. The tapping was continued until no further change in volume was noted.

$$D_t = M / Vt$$

Where,

M is the mass of powder

Vt is the tapped volume of the powder.

Angle of Repose

It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. The angle of repose was determined by the funnel method suggested by Newman. Angle of repose is determined by the following formula

$$\text{Tan } \theta = h/r$$

Therefore $\theta = \text{Tan}^{-1} h/r$

Where,

θ = Angle of repose

h = height of the cone

r = Radius of the cone base.

Compressibility Index

The compressibility index has been proposed as an indirect measure of bulk density, size, shape, surface area, moisture content and cohesiveness of materials because all of these can influence the observed compressibility index.

Carr's compressibility index (%) = $[(D_t-D_b) \times 100] / D_t$

Where,

D_t is the tapped density

D_b is the bulk density

Hauser's ratio

Hausner's ratio is an indirect index of the ease of powder flow. It is calculated by the following formula.

Hausners ratio = D_t/D_b

Where, Dt is the tapped density,

Db is the bulk density.

Post compression studies

Tablet thickness test[8]

Randomly 10 tablets were taken from each formulation trial batch and their thickness was measured using a Vernier caliperse.

Weight variation test[8]

The weight variation test is carried out in order to ensure uniformity in the weight of tablets in a batch. The total weight of 20 tablets from each formulation was determined and the average was calculated. The individual weights of the tablets were also determined accurately and the weight variation was calculated.

Measurement of tablet hardness[8]

The hardness of tablet is an indication of its strength. The force is measured in kg and the hardness of about 3-5 kg/cm2 is considered to be satisfactory for uncoated tablets. Hardness of 10 tablets from each formulation was determined by Monsanto hardness tester.

Friability test[8]

It is measured of mechanical strength of tablets. Roche Friabilator is used to determine the friability by following procedure. Twenty tablets were weighed and placed in Roche Friabilator where the tablets were exposed to rolling and repeated shocks resulting from free falls within the apparatus. After 100 revolutions, tablets are removed, dedusted and weighed again. The friability was determined as the percentage loss in weight of the tablets.

% Friability = (loss in weight / Initial weight) X 100

Disintegration Time

The USP device to rest disintegration was six glass tubes that are "3 long, open at the top, and held against 10" screen at the bottom end of the basket rack assembly. One tablet is placed in each tube and the basket rack is positioned in 1 liter beaker of distilled water at 37± 2^{o}C, such that the tablets remain below the surface of the liquid on their upward movement and descend not closer than 2.5cm from the bottom of the beaker.

Content uniformity

From each batch of prepared tablets, ten tablets were collected randomly and powdered. A quantity of powder equivalent to weight of one tablet was transferred in to a 100 ml volumetric flask, to this 50 ml pH 1.2 was added and then the solution was subjected to sonication for about 2 hrs. The solution was made up to the mark with pH 1.2 buffers. The solution was filtered and suitable dilutions were prepared with pH 1.2 buffer. Same concentration of the standard solution was also prepared. The drug content was estimated by recording the absorbance at 220 nm by using UV-Visible spectrophotometer.

***In vitro* dissolution**

Freshly prepared phosphate buffer (pH 1.2) of 900 ml was placed in each dissolution vessels of dissolution test apparatus (USP, II paddle method). The tablets were placed in the dissolution medium. The temperature of the dissolution medium was maintained at 37± 0.5^{0}C and the paddle was rotated at 50 rpm. 5 ml samples were withdrawn. The sample volume was immediately replaced with the same volume of fresh media as when a sample was taken. The samples withdrawn were filtered, diluted and estimated spectrophotometrically at 220 nm. Cumulative amount of the drug released at each interval was calculated by using standard graph of Solifenacin succinate.

RESULTS AND DISCUSSION

Physical mixture of drug and polymer was

characterized by FTIR spectral analysis for any physical as well as chemical alteration of the drug characteristics, DSC, XRD. From the results, it was concluded that there was no interference in the functional groups as the principle peaks of the Solifenacin succinate were found to be unaltered in the spectra of the drug-polymer physical mixture (Figure No.1, 2and 3).

Pre-compression Studies

All the formulations prepared by both the methods showed the angle of repose less than 30ºC, which reveals good flow property (Table No.2). The loose bulk density and tapped bulk density for the entire formulation blend varied from0.51gm/cm^3 to 0.593 gm/cm^3 and 0.601 gm/cm^3 to 0.692 gm/cm^3 respectively (Table No.2). The results of Carr's consolidation index or compressibility index (%) for the entire formulation blend ranged from 8.89 to 14.84%.

Post-compression Studies

The mean thickness was almost uniform in all the formulations and values ranged from 4.48mm to 4.48 mm. The standard deviation values indicated that all the formulations were within the range (Table No.3).

The hardness values ranged from 3.15 to 3.64 kg/cm^2 for formulations were almost uniform. Tablet hardness is not as absolute strength (Table No.3).

Friability values were found to be within the limit. Thus tablets possess good mechanical strength (Table No.3).

All the tablets passed weight variation test as the average percentage weight variation was within the pharmacopoeial limits of 7.5%. The disintegration time was found to be between 3.40 to 12.50 min.

The drug content (Table No.3) of the tablets was found to be between 98 to 101 %. The results were within the range and that indicated uniformity of mixing. The cumulative percentage drug released by each tablet in the *in vitro* release studies was based on the average drug content present in the tablet. Stability studies for the developed formulations were carried out by storing the selected formulations at 40°C/75% RH up to one month.

Table No.1: General composition of formulation prepared by wet granulation method

S.No	Ingredients	F 1	F 2	F 3	F 4	F 5	F 6	F 7	F 8	F 9
1	Solifenacin succinate	6.66	6.66	6.66	6.66	6.66	6.66	6.66	6.66	6.66
2	Lactose monohydrate	87.3	71.2	80.0	71.8	81.7	80.5	80.0	81.7	80.0
3	Corn starch	5	20	7.5	20	7.5	10	7.5	7.5	7.5
4	HPMC E-5	Nil	Nil	3	Nil	3	Nil	3	3	3
5	Cross povidone	Nil	1	Nil	0.4	Nil	Nil	Nil	Nil	Nil
6	CCS intra granular	Nil	Nil	Nil	Nil	Nil	2	Nil	Nil	Nil
7	Magnesium stearate	1	0.6	0.6	0.6	0.9	0.4	0.6	0.6	0.6
8	Colloidal silicon dioxide	Nil	0.5	0.5	0.5	0.5	0.4	0.5	0.5	0.5
9	Purified water	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S

Table No.2: Results of flow properties of immediate release tablet (F1 to F9)

S.No	Formulation code	Angle of repose(θ)	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Compressibility index (I)	Hausner's ratio
1	F1	30.08	0.56	0.65	14.84	1.17
2	F2	29.8	0.54	0.63	14.28	1.15
3	F3	28.5	0.53	0.62	13.81	1.16
4	F4	28.8	0.52	0.60	13.55	1.17
5	F5	27.6	0.53	0.61	13.31	1.14
6	F6	27.9	0.58	0.63	12.86	1.14
7	F7	26.8	0.55	0.66	12.32	1.15
8	F8	26.6	0.51	0.60	10.55	1.13
9	F9	26.4	0.59	0.69	8.89	1.13

Table No.3: Uniformity of Thickness, Hardness, Friability, Disintegration and Weight variation (F1 to F9)

S.No	Formulation code	Weight Variation (mg)	Uniformity of Thickness (mm)	Hardness (kg/cm^3)	Friability %	Disintegration Time (min)
1	F1	101.6	4.48	3.45	0.50	3.45
2	F2	102.3	4.49	3.55	0.45	3.40
3	F3	101.5	4.49	3.14	0.47	3.50
4	F4	100.1	4.48	3.26	0.58	5.50
5	F5	101.1	4.49	3.64	0.46	6.30
6	F6	101.0	4.48	3.22	0.59	7.50
7	F7	100.1	4.48	3.15	0.46	8.40
8	F8	100.5	4.49	3.15	0.42	9.35
9	F9	98.3	4.49	3.20	0.48	12.50

Table No.4: Comparative dissolution profiles of trial batches with reference product (Vesicare)

S.No	Time (min)	% of Drug Release									
		Innovator	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	10	56.8	69	69.1	47.3	68.4	48.5	59.1	58.9	56.6	56.7
2	15	80.1	86.4	89.2	71.3	90	69.9	74.6	80.8	81.3	80.3
3	30	94.8	89.2	92	94.7	94.4	95	88.5	92.2	95.1	94.4
4	45	94.7	89	93.1	100.8	94.8	96.2	95.3	92.1	96.4	95.8

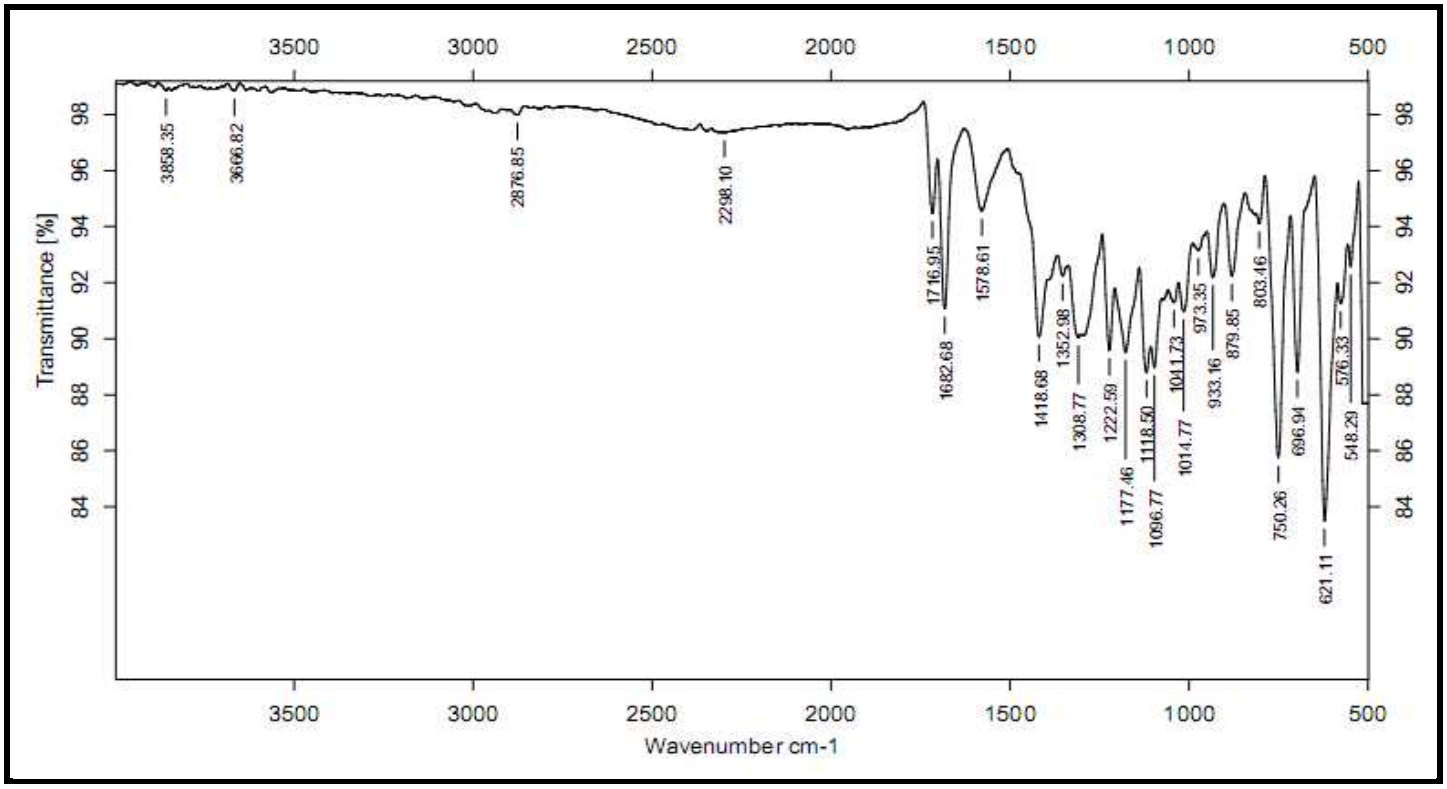

Figure No.1: FT-IR spectra of pure Solifenacin succinate

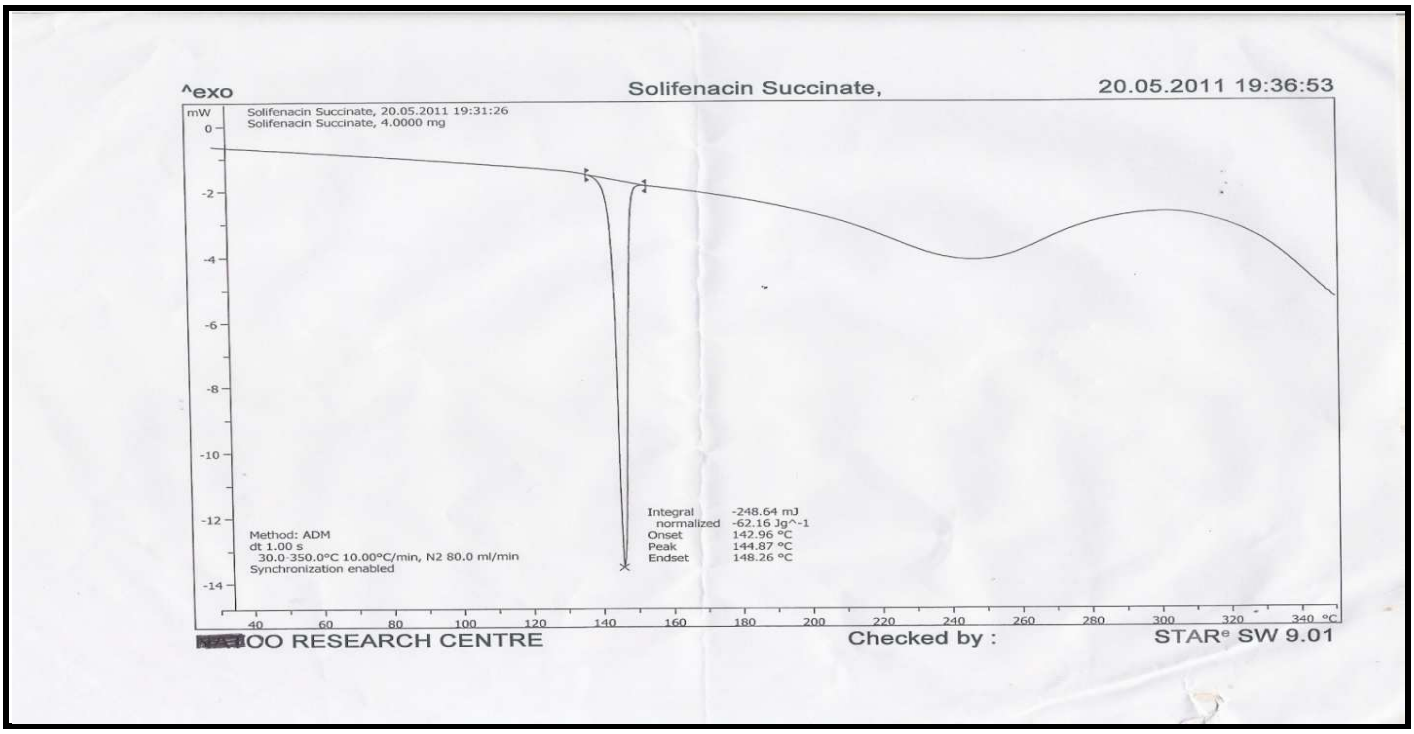

Figure No.2: DSC scan report of pure solifenacin succinate

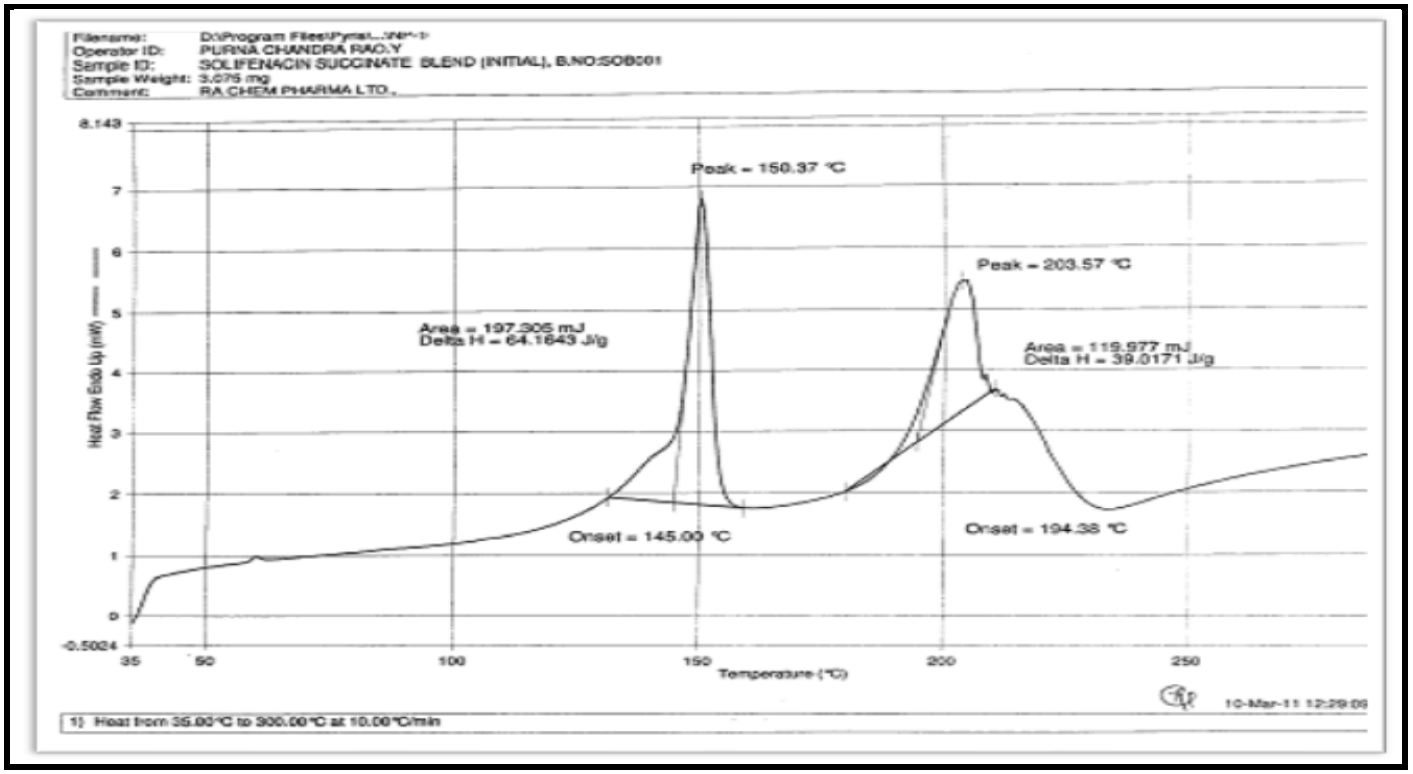

Figure No.3: XRD scan report of drug+excipients

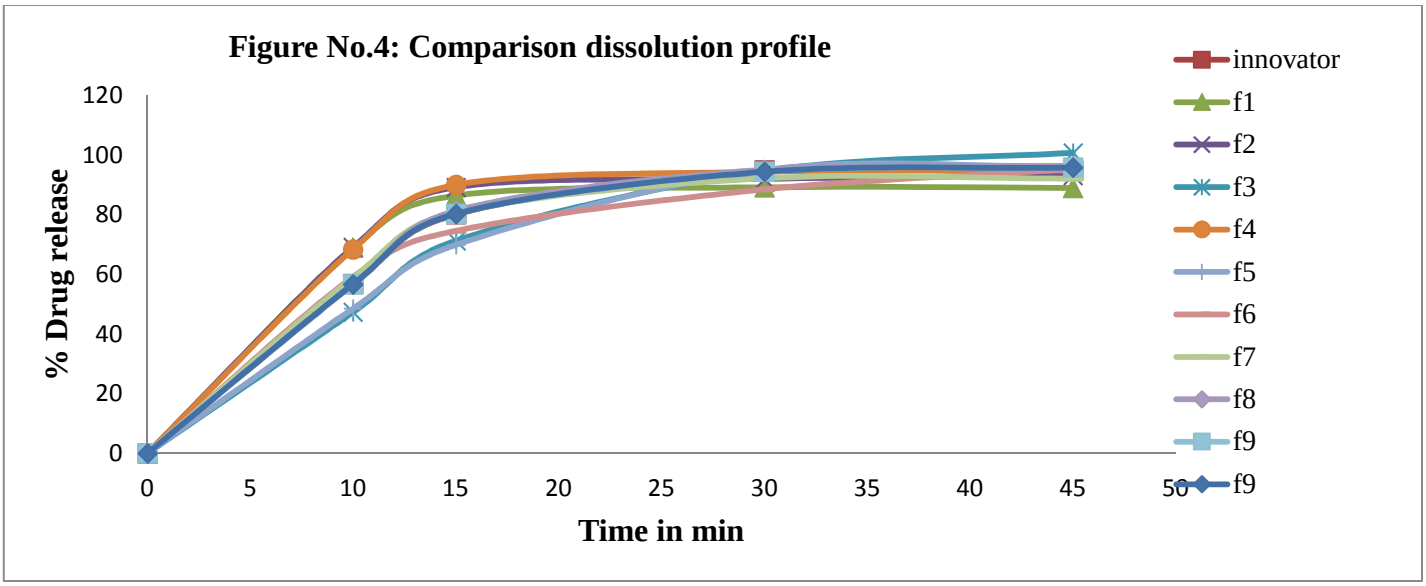

Figure No.4: Comparison of dissolution profile

CONCLUSION

In the present study, solifenacin succinate tablets were prepared successfully by using wet granulation method. Nine formulations were developed on the basis of trial and error method. All the trial formulations were evaluated for pre-compression as well as post compression parameters. The solubility studies for all the excipients including API were conducted and the solubility of solifenacin succinate was freely soluble in water. So that purified water was chosen as solvent for granulating solution. All the excipients were well compatible with each other and also with the API.All the powder characteristics i.e. angle of repose, compressibility index, hausner's ratio were checked for all the trial batches and the flow was found to be good to excellent. All the trial batches were compressed by maintaining the good manufacturing practice. The evaluation studies for compressed tablets were carried out and the results were satisfactory as that of ICH guidelines. *In vitro* dissolution results showed that % of drug release was desirable in formulation trial IX when compared to other formulations. This indicates that the drug released from the formulation IX was effective.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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