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Formulation and In vitro Evaluation of Solifenacin Succinate Fast Dissolving Drug Delivery Systems

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Abstract : The present study was aimed to formulate and evaluate solifenacin succinate fast dissolving drug delivery systems (FDDDs) i.e., fast dissolving tablets (FDTs) and fast dissolving films (FDFs) and comparison of their drug release. Tablet containing drug and excipients were prepared by direct compression and the film by solvent casting method using di-chloromethane and methanol as solvents and HPMC E5 as film forming polymer. Superdisintegrants such as crospovidone (CP), croscarmellose sodium (CCS) and sodium starch glycolate (SSG) alone and also in combinations were incorporated to achieve the aim. Drug excipients interaction studies were carried out by FTIR spectral analysis. The tablets were evaluated for their hardness, wetting time, disintegrating time and dissolution parameters. The film was evaluated for drug content, folding endurance, thickness and in vitro disintegration time. Among all, the tablets having 8% crospovidone met all the evaluation parameters and thus selected as the optimized tablet formulation to compare with film. In vitro drug release of optimized tablet formulation was 95.41% and film was 97.5% in 15 min. Thus film was considered to be the best formulation. We conclude that the fast dissolving drug delivery systems of solifenacin succinate can be successfully prepared which can be a patient friendly dosage form.
Keywords : Fast dissolving tablet, fast dissolving film, crospovidone, croscarmellose sodium, sodium starch glycolate, HPMC E5.

Introduction

Despite of so much of advancements in various delivery systems developed for administration of various drugs through different routes such as oral, parental, transdermal and nasal etc., the oral route is considered as the preferred route of administration which includes painless, ease of administration, patient friendly and so on[1,2]. Oral route of delivery of drugs remains to be the most convenient and preferred route for administration. This

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route of administration has two main challenges such as dysphagia and delivery of unpalatable drugs. To rectify these challenges, innovative drug delivery systems have been developed. Among the novel approaches, fast dissolving drug delivery system[3]plays an important role. The benefits, in terms of patient compliance, rapid onset of action, increased bioavailability, and good stability make these delivery systems popular as a dosage form of choice in the current market[4,5].FDDDS include tablets and films. Fast dissolving tablets are designed in such a way that they disintegrate and then swallowed without the need of water as compared to other conventional dosage form[6]. Fast dissolving tablets[7] can be formulated using various methods. Some of the methods involve increasing the porosity of the tablet and decreasing the disintegration time. Superdisintegrants for the manufacturing will swell or absorb water rapidly to disintegrate the tablets[8,9,10,11]. Due to the above said reason, the drug is absorbed rapidly and may leads to greater bio availability as compared with conventional dosage system. Films are the small polymeric strips which when placed on the mucosal surface rapidly dissolve within a fraction of seconds in order to release the active ingredients without the consumption of water[12,13]. Like other tablets, patients are sometimes non-compliant with FDTs due to fear of choking. Also FDTs are friable and may break during transport and handling. Fast dissolving film is a better alternative to FDTs. FDFs when placed on the tip or the floor of the tongue are instantly wet by saliva. As a result, orally disintegrating films (ODFs) rapidly hydrate and then disintegrate and/or dissolve to release the medication for local and/or systemic absorption.

Solifenacin is a competitive muscarinic receptor antagonist. It is commonly used for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency. The main objective of the present work was to formulate fast dissolving solifenacin succinate tablets by direct compression method and fast dissolving film by solvent casting method and comparison of drug release of optimized fast dissolving tablet formulation with film.

Materials and Methods

Materials

Solifenacin succinate obtained from Hetero Chemicals, Hyderabad. Sodium starch glycolate, crosspovidone, croscarmellose sodium, mannitol, magnesium stearate, talc, propylene glycol were obtained from SD-FINE Chem. Limited, Mumbai. HPMC E5 and aspartame were obtained from LobaCheme, Mumbai. All other materials used were of pharmaceutical grade.

Calibration curve

Accurately weighed solifenacin succinate was dissolved to make the solution in range of 10 to 50µg/ml using phosphate buffer pH6.8. Absorbance of each concentration was measured using UV Spectrophotometer (Shimadzu) at 253 nm and the absorbance was plotted against concentration of drug solution.

Method

Preparation of mixed blend of drug and excipients

All the materials were passed through sieve no 60. Required quantity of each ingredient was taken for each specified formulation (given in Table1) and all the ingredients were subjected to grinding to a required degree of fineness (except magnesium stearate and talc). The powdered blend was evaluated for flow properties.

Table 1. Composition of fast dissolving tablets of solifenacin succinate

S.No	Ingredient (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Solifenacin succinate	5	5	5	5	5	5	5	5	5
2	SSG	6	-	-	8	-	-	4	-	4
3	CP	-	6	-	-	8	-	4	4	-
4	CCS	-	-	6	-	-	8	-	4	4
5	Mannitol	86	86	86	84	84	84	84	84	84
6	Aspartame	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
7	Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Total weight(mg)		100	100	100	100	100	100	100	100	100

Compression of tablets by using direct compression technique[14,15]

Finally magnesium stearate and talc were added to the prepared blend. The mixed blend of drug and excipients was compressed into tablets weighing 100mg using flat faced punches of 7mm diameter in a rotary tablet press (Remek –16 station). A minimum of 50 tablets were prepared for each batch.

Evaluation of Tablets

Compatibility studies[16]

Compatibility between the drug and the excipients were studied using Fourier Transform Infrared (FTIR) spectrophotometer (Shimadzu) using KBr disc method.

Physical characterization[17]

The stored tablets were analysed for the different parameters such as weight variation, hardness and percentage friability.

Wetting time[18]

This parameter is very much useful in predicting the disintegration time of the tablet. Here the tablet was placed on a filter paper & that was placed in a petridish containing 10 mlof water. The time taken for complete wetting of the tablet was noted and recorded.

Drug content[19]

Randomly selected five tablets from each batch were weighed and crushed to make a powder. An amount of powder equivalent to 5 mg of solifenacin succinate was weighed and dissolved in a 50 ml standard flask containing buffer solution pH 6.8 and allowed to extract the contents. After 30 min, the solution was filtered and suitable dilutions were made. Suitably diluted solution was undergone for measuring the absorbance and the drug content was tabulated.

In vitro disintegration time[20]

Disintegration time measures the time taken to disintegrate the tablet. Six tablets were collected in a random from each batch. Each tablet from each batch was placed in the disintegration apparatus (Labindia) as specified in the Indian Pharmacopoeia (IP). Buffer solution pH 6.8 was used as the medium which was maintained at a temperature of 37±2ºC.

In vitro dissolution studies[21]

Dissolution test was carried out using dissolution apparatus USP Type II (Labindia)using buffer pH 6.8 as the dissolution medium, maintained at a temperature of 37±0.5ºC. Aliquot amount of solution was withdrawn in every 3 min. The filtered solution was analyzed for the drug concentration by measuring absorbance at 253 nm using UV spectrophotometer. The measured absorbance was tabulated and the amount of drug present was recorded.

Table 2. Composition of solifenacin succinate fast dissolving film

S.No	Ingredient	Quantity (mg)
1	Solifenacin succinate	5.0
2	HPMC E5	10.0
3	Propylene glycol	0.3 ml
4	Citric acid	2.0
5	Aspartame	2.5
6	Methanol: DCM (1:1)	20.0 ml

*DCM: dichloromethane

Preparation of film by solvent casting method

Films were prepared by solvent casting method according to the formula given in Table 2. The polymeric solution of HPMC was prepared by using dichloromethane and methanol in the ratio of 1:1 with continuous stirring. After continuous stirring the solution was left undisturbed for three to four hours to remove all the air bubbles and swelling of the polymer. Accurately weighed quantity of drug, plasticizer and all other excipients were separately dissolved in solvent in another beaker. After complete swelling of the polymer, drug-plasticizer and all other excipient solutions were added and mixed thoroughly, and the volume was made up. The solution was casted on a petridish (diameter 9 cm) and dried at 45ºC in hot air oven for 45 min. The film was carefully removed from the petridish, checked for any imperfections and cut into the required size to deliver the equivalent dose (2x 2 cm^2) per strip. The strips were finally packed in an aluminum foil.

Evaluation of FDFs[22,23,24,25]

Weight variation

For weight variation three films of the formulation were taken, weighed individually on digital balance then average weight was calculated**.**

Thickness measurement

The thickness of each film was measured at five different locations (center and four corners) using Vernier calipers micrometer(Grovers Group). Data was represented as a mean ± SD of triplicate determinations.

Determination of moisture uptake

Films were cut into 2× 2 cm^2 strips (4 cm^2). The moisture uptake by the films was determined by exposing them to 75% relative humidity (RH) at room temperature (25±2°C) for one week. The uptake of moisture by the films was measured and calculated as percent increase in weight.

Tackiness evaluation

Tack is the tenacity with which the film adheres to an accessory that has been pressed into contact with the film. Tackiness evaluation was carried out by gently pressing the film between fingertips and results were noted in qualitative terms as tacky or non-tacky.

Folding endurance

The folding endurance of the film was determined by repeatedly folding one film at the same place till it breaks. The number of times of film could be folded at the same place without breaking was noted; which gave the value of the folding endurance.

In vitro disintegration time

The film size required for dose delivery (2× 2 cm^2) was placed in a glass petri dish containing 10 ml of distilled water. The time required for the film to break was noted as in vitro disintegration time. Test was conducted in triplicates.

Drug content determination

The films (2×2cm^2) were cut and added to a beaker containing 100ml of phosphate buffer of pH 6.8. The medium was stirred with magnetic bead. The contents were filtered using Whatmanfilter paper and the filtrate was examined for the drug content against the reference solution consisting of placebo films at 253nm spectrophotometrically. The experiment was repeated to validate the result.

In vitro dissolution study

The in vitro dissolution test was performed using the USP dissolution apparatus II (paddle with sinker). The dissolution studies were carried out at 37±0.5°C; with stirring speed of 50 rpm in 900 ml phosphate buffer of pH 6.8. Film size required for dose delivery (2×2cm^2) was used. 5ml aliquot of dissolution media was collected at time intervals of 1, 3, 6, 9, 12 and 15 minand replaced with equal volumes of phosphate buffer. The collected samples were filtered through 0.45 μm membrane filter and the concentration of the dissolved

solifenacin succinate was determined using UV visible spectrophotometer at 253 nm. The results were presented as an average of three such concentrations.

Results and Discussion

Preparation of tablets and films

Direct compression method was used for the manufacturing of fast dissolving tablet and solvent casting method for FDF of solifenacin succinate. Primary evaluation tests of the tablets and film were carried out and from the results, it is clear that the techniques adopted are suitable to the process.

Compatibility studies

Compatibility studies were carried out to study the chemical interaction between drug and the excipients. After interpreting the FTIR spectra (Figure1- 3), it was found that the drug is compatible with the excipients. The FTIR study concluded that the absorption present in solifenacinsuccinate were 3300±100 (O-H), 3000±100 (C- H), 2200±100 (-C≡ C-), 1700±100 (C= O), 1600±50 (C= O), 1500±50 (C= C),1400±50 (C= C) and 1200±50 (C- O). These all absorption bands were present on the formulation. So this clearly suggests that the drug remains in the same form even in its formulations indicating that there is no interaction between the drug and polymer used for the study.

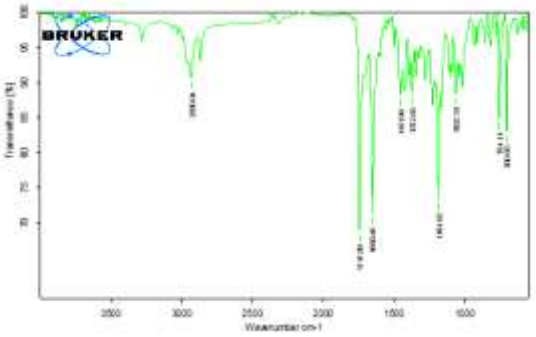

Figure 1. FT-IR spectrum of pure solifenacin succinate

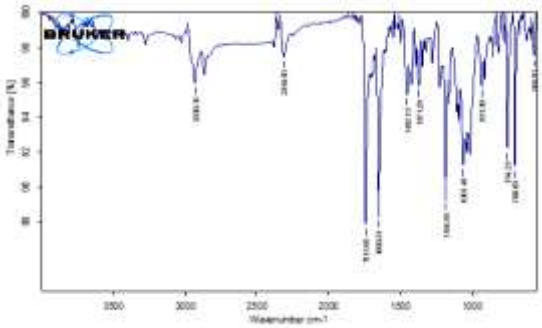

Figure 2. FT-IR spectrum of physical mixture of formulation F5

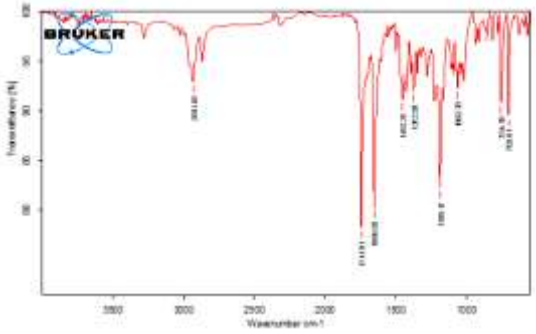

Figure 3. FT-IR spectrum of physical mixture of solifenacin succinate and HPMC E5

Physical characterization

The prepared tablets were taken for hardness evaluation using Monsanto hardness tester. From the results, the hardness of the tablets was found in the range of 2.5-3.0kg/cm^2, proved for its adequate strength. Weight variation test performed for each tablet and the obtained report showed that the tablets having the weights in the range of 95 to 105 mg. All the tablets passed the weight variation test as the average percentage weight variation is within the limit of IP standards. Thickness of the tablets was measured and the obtained report proved that all the tablet having uniform thickness. All the tablets physical parameters were postulated in Table 4.

Wetting time

Wetting time was closely related to the inner structure of the tablet. The wetting time of the prepared formulations was found to be in the range of 20 to 50 sec. The formulation F5 showed the wetting time 20 secthat facilitates faster dispersion in the mouth (Table 4 and Figure 4).

Table 3. Evaluation of the powder blend

Code	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Compressibility index (%)	Hausner'sratio	Angle of repose (θ°)
F1	0.2013±0.001	0.2439±0.001	17.46±1.91	1.21±0.02	30.34±1.72
F2	0.2068±0.006	0.2459±0.004	15.90±2.11	1.18±0.01	27.21±1.58
F3	0.2000±0.004	0.2459±0.001	18.66±1.74	1.22±0.02	28.98±1.91
F4	0.2000±0.009	0.2479±0.008	19.33±1.63	1.23±0.01	29.29±1.33
F5	0.2013±0.003	0.2400±0.004	16.12±1.06	1.19±0.03	29.74±2.01
F6	0.2143±0.001	0.2727±0.001	21.42±1.69	1.27±0.01	31.56±2.31
F7	0.2173±0.003	0.2586±0.006	17.13±1.97	1.19±0.02	30.34±1.53
F8	0.2143±0.002	0.2678±0.004	19.99±2.03	1.24±0.01	32.22±1.27
F9	0.2000±0.004	0.2500±0.005	20.00±1.38	1.25±0.01	30.05±1.49

Mean ± S.D., n=3

Table 4. Evaluation of solifenacin succinate fast dissolving tablets

Code	Wetting time(sec)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Disintegration time (sec)	Weight variation	Drug content (%)
F1	50 ±1.6	1.63 ±0.05	3.0 ±0.11	0.50	61 ±1.7	101.54 ±1.3	99.36 ±0.94
F2	27 ±1.4	1.38 ±0.03	2.5 ±0.14	0.74	30 ±0.9	99.68 ±1.5	98.68 ±0.66
F3	37 ±1.8	1.56 ±0.06	2.9 ±0.11	0.72	45 ±1.9	100.45 ±2.2	99.09 ±0.73
F4	35 ±1.4	1.62 ±0.09	2.5 ±0.13	0.35	41 ±2.0	101.32 ±1.3	99.71 ±0.93
F5	20 ±1.1	1.68 ±0.05	3.0 ±0.11	0.50	25 ±1.4	100.45 ±1.5	99.57 ±0.99
F6	30 ±1.3	1.56 ±0.07	3.0 ±0.12	0.53	37 ±1.1	100.55 ±1.9	98.29 ±0.58
F7	43 ±1.9	1.38 ±0.08	2.8 ±0.14	0.53	50 ±2.1	102.58 ±1.1	99.03 ±0.77
F8	23 ±1.4	1.63 ±0.04	2.7 ±0.11	0.58	29 ±1.9	99.39 ±1.2	99.12 ±0.42
F9	32 ±1.5	1.86 ±0.06	2.7 ±0.11	0.51	39 ±1.7	99.98±1.3	98.84 ±0.29

Mean ± S.D., n=3

Drug content

The samples were analyzed and the percentage drug content was found out. The report reveals the drug content in the range of 98.29– 99.71% of the solifenacin succinate (Table 4).

Film evaluation

Film thickness was checked by using Vernier caliper. The thickness of the film was found to be 0.15mm. The films were evaluated for the uniformity of dispersion in which all the films were dispersed in few seconds in purified water. Drug content was found to be 95% and folding endurance was found to be 76.All the prepared films were found to be non-tacky.Weight variation was found to be 30.5±1.34 mg. It was observed

that in vitro disintegration time as 30±2.6 sec. The prepared film formulations were assayed for drug content.Results of drug content showed the uniformity of the drug and less loss of drug content. The various results are reported in Table 5.

Table 5.Physico chemical characteristics of the prepared fast dissolving film

Code	Weight (mg)	Thickness (mm)	Disintegration time(sec)	Drug content (%)	Folding endurance	% Moisture uptake
Film	30.5±1.34	0.15±0.007	30±2.6	96.35±2.64	76±4	0.46±0.001

Mean ± S.D., n=3

In vitro disintegration time

In vitro disintegration time is measured by the time taken to undergo complete disintegration. Rapid and uniform disintegration of tablets were observed in all the formulations. The report shows the disintegration time for all the formulations in the range of 25 to 61 sec fulfilling the official standards. Based on the invitro disintegration time, the formulation F5 showed a fast disintegration time of 25 sec. Thus the formulation can be selected as the ideal formulation.The values were given in Table 4 and Figure 5.

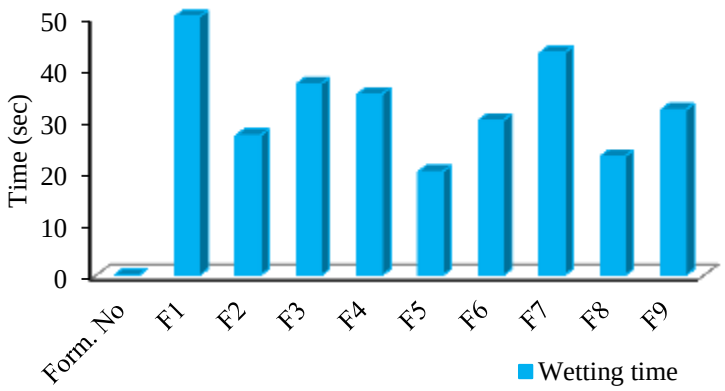

Figure 4. Plot of comparison of wetting time (F1-F9)

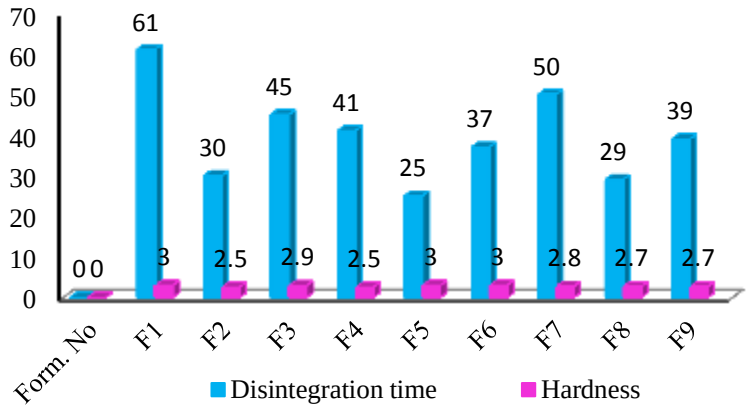

Figure 5. Plot of comparative disintegration time (sec) and hardness (kg/cm^2)

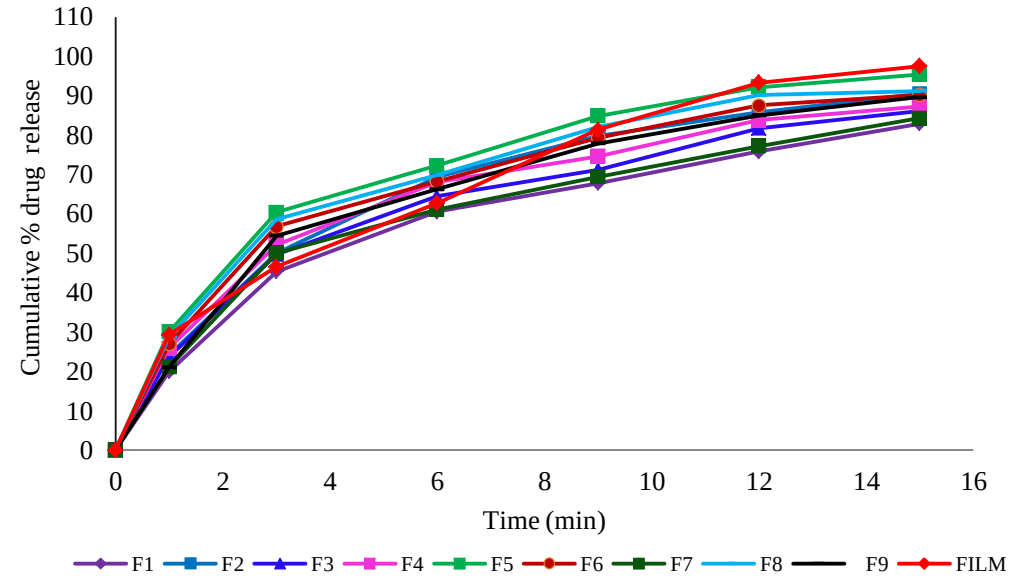

Figure 6. Cumulative % drug release vs time plot of F1-F9 and FILM

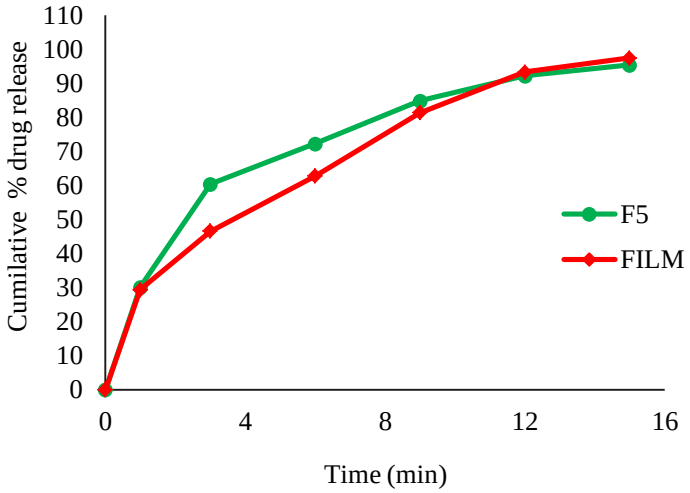

Figure 7. Cumulative % drug release vs time plot of F5 and FILM

In vitro dissolution studies

In vitro dissolution studies were also carried out to optimize the ideal formulation. From the parameters the formulation F5 showed good release profile for the time specified. The in vitro release profiles of all the formulations and FILM were given in the Table 6 and the graphs were given in the Figure 6, 7. The uniformity in the release profile may be due to the presence of superdisintegrants in the correct ratio for the formulation. Thus it is selected as an ideal formulation. Finally F5 was selected as an optimized formulation as it has shown better release than other tablet formulations.The percentage drug release of F5 and FDF at the end of 15 min was found to be 95.41% & 97.50% respectively. Comparatively fast dissolving film showed better release. The drug release order of fast dissolving tablets and film are given as follows film > F5 > F8 > F2 > F6 > F9 > F4 > F3 > F7 > F1.

Table 6.Invitro drug release of prepared solifenacin succinate FDTs and film

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9	FILM
1	20.06±0.23	24.19±0.23	23.72±0.24	25.96±0.43	30.14±0.67	27.01±0.32	21.16±0.34	28.79±0.32	21.11±0.43	29.37±0.11
3	45.34±0.31	50.12±0.01	49.75±0.35	52.22±0.56	60.43±0.34	56.84±0.31	50.05±0.45	58.62±0.23	54.45±0.42	46.61±0.02
6	60.59±0.25	69.42±0.12	64.50±0.02	68.07±0.67	72.30±0.23	68.25±0.56	61.14±0.23	69.89±0.43	66.29±0.43	62.75±0.11
9	67.83±0.02	79.71±0.34	71.20±0.43	74.66±0.23	84.83±0.35	79.32±0.58	69.45±0.43	82.01±0.12	77.91±0.21	81.35±0.21
12	75.85±0.34	85.83±0.41	81.79±0.24	83.78±0.45	92.21±0.45	87.53±0.45	77.22±0.21	90.17±0.22	85.03±0.31	93.31±0.31
15	82.93±0.45	90.57±0.23	86.06±0.56	87.22±0.45	95.41±0.34	90.26±0.78	84.29±0.32	91.21±0.32	89.63±0.31	97.50±0.34

Mean ± S.D., n=3

Kinetics of drug release

Based on mathematical models, it was concluded that the release profile of the F5 fitted best to first order with R^2 value of 0.991. The release profile of the film best fitted to Higuchi with R^2 value of 0.995. As the 'n' value of film for the Korsmeyer-Peppas model was found to be less than 0.5, it follows Fickian diffusion. The Higuchi and Korsmeyer plots for FILM formulation were given in Figure 8, 9.

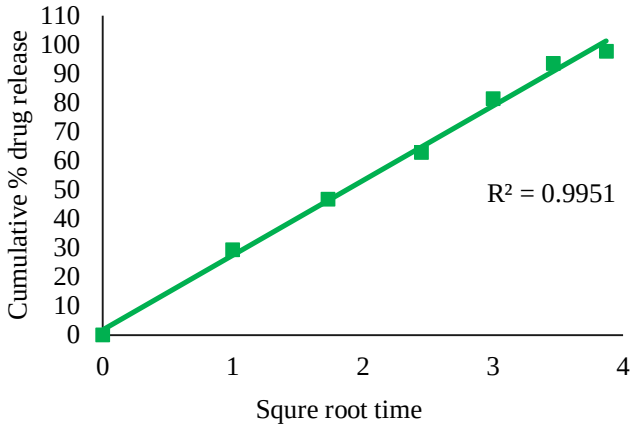

Figure 8. Cumulative % drug release vs √T plot of FILM

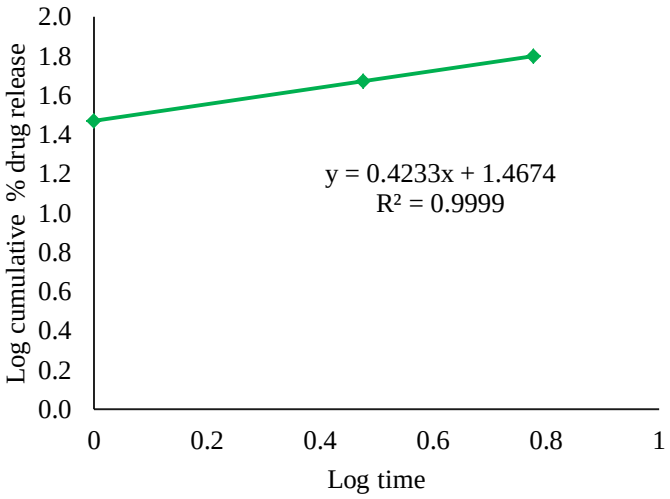

Figure 9. Log cumulative %Drug release Vs log time plot of FILM

Conclusion

In the present work efforts have been made to prepare and evaluate FDTs of solifenacin succinate with different concentrations of superdisintegrants SSG, CCS, CP by direct compression technique and FDF by solvent casting method. The FDTs found to have excellent physical characters. The superdisintegrants were also found to be compatible with the other excipients of the formulation as well as with drug, which is evident from the FT-IR values. The results revealed that as the concentration of superdisintegrant was increased, it was found that the disintegration time decreased and % drug release increased. The drug release from all batches was found to be concentration dependent. Release profile of F5 having 8% CP and film were found to have maximum release of 95.41 % and 97.50% respectively at the end of 15min. Drug release kinetics shown that film follows Fickian diffusion release mechanism as 'n' value was less than 0.5. Out of all FDTs prepared by direct compression, FDF prepared by solvent casting method, FDF found to be the best formulation. The rank order for best formulation is as follows film> F5 > F8 > F2 > F6 > F9 > F4 > F3 > F7 > F1. Hence the formulation of film fulfills the objective of the present study. Thus we conclude that the FDT and FDF of solifenacin succinate can be successfully prepared using conventional methods and equipment's and can be a patient friendly dosage form for the treatment of contraction of overactive bladder with urge incontinence.

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