Original Article

Optimization of Fast-dissolving Tablets of Ledipasvir-sofosbuvir Inclusion Complexes by Design of Experiments

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ABSTRACT

Background: Fast-dissolving tablets (FDTs) were aimed to be developed for the latest approved combination drugs for Hepatitis-C treatment, Ledipasvir (LDV) and sofosbuvir (SBV) which suffered with poor water solubility. **Materials and Methods:** Cyclodextrin (CD) complexation was done for the drugs to improve their solubility. The optimized CD complexes were taken for developing FDTs to improve dissolution limited bioavailability of these drugs. FDTs were developed by adopting design of experiments approach using Design Expert software. Type of β-CD, type of disintegrant and concentration of disintegrant were taken as the factors. Disintegration time, time for 90% dissolution of LDV and SBV were taken as the responses. The prepared tablets as per the selected experimental design were evaluated for the responses and also other characteristics like tensile strength, packing fraction, wettability. The results were analyzed by ANOVA and numerical optimization was performed with the desirability of minimizing all the responses. **Results:** All the selected factors were found to influence disintegration and dissolution times significantly. Dimethyl β-CD, croscarmellose sodium at 8% w/w was obtained as the optimized combination of the factors for the FDTs. The FTDs at this optimized combination of the factors were found to have 79.6 sec of DT, 17.72 and 13.68 min. of time for 90% dissolution of LDV and SBV respectively. **Conclusion:** These results which were significantly much better than those of the marketed tablets indicated that the FTDs were successfully developed using Design of experiments.

Keywords: Fast dissolving tablets, Hepatitis-C, Ledipasvir, Sofosbuvir, Optimization.

Submission Date: 21-02-2022;
Revision Date: 24-06-2022;
Accepted Date: 08-08-2022.

DOI: 10.5530/001954641530

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INTRODUCTION

Leldipasvir (LDV) and sofosbuvir (SBV) are the recently approved combination drugs for the treatment of Hepatitis-C. These drugs are used at the fixed dose combination of 90 mg of LDV and 400 mg of SBV.[1,2] LDV is practically insoluble and SBV is slightly soluble in water,[3] and hence both these drugs have limited bioavailability because of poor dissolution. Hence, a dosage form which can improve the dissolution of these drugs is necessary. The literature on dosage form development of these drugs is very scarce as these are new drugs. Only one article was published which was on the fast-dissolving tablets for LDV only.[4] Hence, there is a great scope for performing dosage form development on these two drugs combination.

Tablets have the advantages of good stability and patient convenience but they suffer poor dissolution and bioavailability when compared to other dosage forms like suspensions. Whereas suspensions have considerable disadvantages like poor physical and chemical stability when compared to tablets. A dosage form with combined advantages of both the tablets and the suspensions is always desirable. Fast dissolving tablets (FDTs) exhibit rapid disintegration and dissolution upon

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administration. These properties make them similar to suspensions yet having good stability as they are tablets by form.[5-6] These FDTs are particularly much desirable for drugs with dissolution limited bioavailability problems.[7] Good amount of research work was published in this regard exploring various techniques like lyophilization, co-grinding,[8] and sublimation,[9] before subjecting to compression. But the lyophilization and sublimation techniques are reported to have physical stability issues and the co-grinding technique showed limited improvement in the dissolution.[9] Further, the FDTs prepared by lyophilization and sublimation techniques are bigger in sizes because of the porous nature making them less suitable for high dosed drugs.[10] This literature indicates still there is a scope for exploring techniques for developing FDTs for high dosed drugs.

In this research work, FDTs were aimed to develop through cyclodextrin (CD) complexation of the drugs followed by their direct compression using superdisintegrants. Cyclodextrin complexation can increase the solubility and hence aid for the dissolution of the drugs from the FDTs.[11,12] Further, the complexes obtained after solvent evaporation method can have improved compressibility so as to make these high dosed drugs suitable for direct compression.[13] Hence, in this work inclusion complexes were prepared using three types of CDs at different ratios. The optimized complexes with high solubility and suitable compressibility were considered for the development of the FDTs. The FDTs were planned to develop using design of experiments (DoE),[14] using Stat Ease Design Expert software. Three formulation factors viz. type of CD, type of disintegrant and concentration of disintegrant were taken as the factors. Disintegration time, time for 90% dissolution of LDV and SBV were taken as the responses. Finally, numerical optimization was performed to identify optimized combination of the factors so as to obtain FDTs with rapid disintegration and dissolution.

MATERIALS AND METHODS

Materials

LDV and SBV were acquired from Hetero Drugs Pvt. Ltd, Visakhapatnam; Hydroxypropyl-β-cyclodextrin (HP-β-CD) and Dimethyl-β-cyclodextrin (Dimethyl-β-CD) were purchased from Sigma Chemicals Co., Mumbai; Sodium starch glycolate (SSG), croscarmellose sodium (CCS), crospovidone (CP), microcrystalline cellulose (MCC), mannitol were purchased from SD Fine Chemicals, Mumbai; All other chemicals of analytical grade were used.

Methods

Preparation of inclusion complexes of LDV and SBV (LSICs)

Inclusion complexes for the combined LDV and SBV were prepared using three different cyclodextrins (CDs) viz. β-cyclodextrin (β-CD), HP-β-CD and Dimethyl-β-CD. Three molar ratios of drug to CD were taken at 1:0.05, 1:0.1 and 1:0.2 with each type of CD. Inclusion complexes were prepared for these nine combinations using solvent evaporation method.[15] Mixture of Dimethyl sulfoxide (DMSO) and isopropyl alcohol at 1:1 ratio was taken as the solvent. 900 mg 1.01 mM) of LDV and 4000 mg (7.56 mM) of SBV were taken and dissolved in the solvent mixture. Then cyclodextrins corresponding to the selected molar ratios with that of the drugs mixture were taken and dissolved into the drug solution. The resultant mixture was subjected to evaporation using Rotavapor operated at a temperature of 60°C and a pressure of 200 mmHg. After complete evaporation of the solvent, the resultant powdered LSICs were collected and stored properly for further use.

Characterization of the LSICs

Solubility studies

All the nine LSICs formulations along with the pure drugs were subjected to equilibrium solubility studies using shake-flask method.[16] After 24 hr, the mixtures were filtered and the clear solutions were estimated for the solubility of LDV and SBV spectrophotometrically.

Powder X-ray diffraction (PXRD) studies

The pure drugs mixture and the LSICs which showed maximum solubility were subjected to PXRD studies. The physical state of the LDV and SBV in the inclusion complexes can be using these studies. These studies elucidate possible mechanism of solubility enhancement from the formed inclusion complexes. The PXRD spectra of the LSICs with maximum solubility were compared with those of the pure drugs.

Micromeritic Properties

The LSICs are further aimed to be developed into FDTs so that micromeritic properties are important to be determined. The optimized LSICs with maximum solubility was passed through sieve # 60 and then studied for bulk density, tapped density, Carr's compressibility index, Hausner's ratio and angle of repose.[9] The LSICs were mixed with 1% w/w glidant and again the above micromeritic properties were determined.

Development of fast dissolving tablets for the LSICs

The LDV and SBV fast dissolving tablets (LS-FDTs) were developed by taking the optimized LSICs using direct compression method. This development and further optimization was carried out by adopting statistical design of experiments (DoE) approach using Stat Ease Design Expert software.

Experimental Design

Miscellaneous factorial design under response surface methodology,[17] was selected as the experimental design. Three different formulation factors were considered viz. type of CD in the LSIC (Factor A: dimethyl-β-CD and HP-β-CD); type of superdisintegrant (Factor B: crospovidone (CP), croscarmellose sodium (CCS) and sodium starch glycolate (SSG)) and concentration of superdisintegrant (Factor C: 4, 6 and 8% w/w). Miscellaneous factorial design was selected because all the three chosen factors were not having same number of levels. The factor A was taken as two levels and the factors B and C were taken each at three levels. So, a 2x3x3 factorial design under response surface methodology was selected as the factorial design. The responses should indicate clearly describe the desired quality characteristics of the developing product. Hence, for the FTDs developing in this work, disintegration time (Response 1: DT) and time for dissolution of 90% (T90) of the dose of both the drugs (Response 2: LDV-T90; and Response 3: SBV-T90) were selected as the responses. According to the selected design, all the 18 possible combinations of the selected factors and their levels required for the development of the FDTs were shown in the Table 1.

Preparation of the FDTs

The LSICs with maximum solubility which were those containing Dimethyl-β-CD and HP-β-CD at 1:0.2 ratio were chosen for the preparation of tablets. The formulation compositions for all the 18 tablets were shown in the Table 2. The LSICs equivalent to 90 mg of LDV and 400 mg of SBV were taken and mixed with microcrystalline cellulose (MCC), povidone (PVPK15) as the binder, superdisintegrant and mannitol after passing through sieve #60. All these powders were mixed thoroughly in a mortar and pestle. Finally magnesium stearate and talc were added and mixed. The final pre-compressed blends were studied for their flowability and compressibility. Finally the blends were subjected to compression in a 12 mm die cavity using rotary tablet compression machine. The obtained tablets were stored properly for further studies.

Table 1: Combination of the three factors and their levels for the selected general 2x3x3 factorial design.

Sl. No.	Run order	Formulation code given	Levels of the factors		
			A: Type of β-CD	B: Type of SDis.	C: SDis. Conc.
1	9	F1	Methyl β-CD	CP	4
2	6	F2	Methyl β-CD	CP	6
3	17	F3	Methyl β-CD	CP	8
4	1	F4	Methyl β-CD	CCS	4
5	2	F5	Methyl β-CD	CCS	6
6	12	F6	Methyl β-CD	CCS	8
7	16	F7	Methyl β-CD	SSG	4
8	15	F8	Methyl β-CD	SSG	6
9	4	F9	Methyl β-CD	SSG	8
10	5	F10	HP β-CD	CP	4
11	7	F11	HP β-CD	CP	6
12	11	F12	HP β-CD	CP	8
13	13	F13	HP β-CD	CCS	4
14	8	F14	HP β-CD	CCS	6
15	3	F15	HP β-CD	CCS	8
16	18	F16	HP β-CD	SSG	4
17	10	F17	HP β-CD	SSG	6
18	14	F18	HP β-CD	SSG	8

β-CD: β-cyclodextrin; HP: Hydroxypropyl; SDis.: Super-disintegrant; Conc.: Concentration in % w/w; CP: Crospovidone; CCS: Croscarmellose sodium; SSG: Sodium starch glycolate.

Characterization studies of the FDTs

Physical characterization studies

Weight variation, friability, disintegration were performed referring to the procedure given in Indian pharmacopoeia. Tensile strength was performed according to the standard procedure reported by Pitt KG *et al*.[18] Packing fraction (P_f) indicates the degree of consolidation of tableting powder after compression. It can be calculated using the equation.[19]

$$P_f = \frac{w}{\pi r^2 t \rho}$$

where, w – weight of tablet; r and t are radius and thickness of tablet; and ϱ is the true density of the tableting powder. Porosity can be calculated by subtracting the P_f value from 1.

Wetting time

This test was performed referring to the general procedure as reported by Gupta B *et al*.[20] Rosaline dye was placed on a tablet which was then kept in a petri

Table 2: Formulation composition of ODTs of formulations F1 – F18.

Sl. No.	Formulation	Quantity in mg per tablet												
		LDV	SBV	Methyl β-CD	HP β-CD	CP	CCS	SSG	PVP K15	MCC	Mannitol	Mg. Stearate	Talc	Total
1	F1	90	400	226	--	38	--	--	47.5	110.5	28.5	4.75	4.75	950
2	F2	90	400	226	--	57	--	--	47.5	91.5	28.5	4.75	4.75	950
3	F3	90	400	226	--	76	--	--	47.5	72.5	28.5	4.75	4.75	950
4	F4	90	400	226	--	--	38	--	47.5	110.5	28.5	4.75	4.75	950
5	F5	90	400	226	--	--	57	--	47.5	91.5	28.5	4.75	4.75	950
6	F6	90	400	226	--	--	76	--	47.5	72.5	28.5	4.75	4.75	950
7	F7	90	400	226	--	--	--	38	47.5	110.5	28.5	4.75	4.75	950
8	F8	90	400	226	--	--	--	57	47.5	91.5	28.5	4.75	4.75	950
9	F9	90	400	226	--	--	--	76	47.5	72.5	28.5	4.75	4.75	950
10	F10	90	400	--	264	38	--	--	47.5	72.5	28.5	4.75	4.75	950
11	F11	90	400	--	264	57	--	--	47.5	53.5	28.5	4.75	4.75	950
12	F12	90	400	--	264	76	--	--	47.5	34.5	28.5	4.75	4.75	950
13	F13	90	400	--	264	--	38	--	47.5	72.5	28.5	4.75	4.75	950
14	F14	90	400	--	264	--	57	--	47.5	53.5	28.5	4.75	4.75	950
15	F15	90	400	--	264	--	76	--	47.5	34.5	28.5	4.75	4.75	950
16	F16	90	400	--	264	--	--	38	47.5	72.5	28.5	4.75	4.75	950
17	F17	90	400	--	264	--	--	57	47.5	53.5	28.5	4.75	4.75	950
18	F18	90	400	--	264	--	--	76	47.5	34.5	28.5	4.75	4.75	950

plate containing 6 mL of water. Then time required to develop red color on the surface of the tablet was taken as the wetting time.

Dissolution Studies

The dissolution test was conducted according to the USFDA suggested method. 1.5% polysorbate 80 in 10 mM potassium phosphate buffer with 0.0075 mg/mL butylated hydroxytoluene with a pH 6.0 of 900 mL was taken as the dissolution medium in the paddle type apparatus that was rotated at 50 rpm. The tablets in the dissolution vessels and samples were drawn for every five minutes for a period of 30 min. After suitable dilutions, the samples were analyzed for the amount dissolved for both the LDV and SBV spectrophotometrically. The obtained dissolution data was subjected to zero-order and first-order kinetic models to identify the order of dissolution kinetics and also to calculate T90% values.

Design Validation and Optimization

The suitability of the selected model to understand the influence of the factors on the responses and to identify whether the factors have significant effect on the responses was studied by ANOVA test. Upon successful validation, optimization was performed using desirability functions approach. The desirability criteria were set as minimizing all the three response so that the product can have rapid disintegration and dissolution. Numerical optimization was performed and the best combination of the factors having maximum desirability was identified.[17] All this validation and optimization was done using the Design Expert software.

RESULTS AND DISCUSSION

Inclusion complexes of LDV and SBV

The inclusion complexes (LSICs) were prepared with three different cyclodextrins using solvent evaporation method. The product obtained were free flowing powders which could be due to the evaporation under very low pressure caused the removal of the solvent completely. The obtained LSICs were first subject to solubility studies and the results were shown in Table 3. These results indicated that the efficiency in increasing the solubility of the three CDs was found to be in the order of β-CD < HP-β-CD < dimethyl-β-CD. This could be attributed to their order hydrophilicity and water of solubility.[21] But, the solubilities of the complexes with the HP-β-CD and Dimethyl-β-CD were almost found to be similar and significantly very high than the corresponding complexes prepared with β-CD. Further, in the LSICs with a particular CD, the solubility was found to be increased with increasing the amount of the CD. This is obvious and could be due to the increasing availability of the host molecules at

Table 3: Results of solubility studies for the prepared inclusion complexes for the combination of LDV+SBV.

Sl. No.	Drug form	Drug: Carrier Ratio	Solubility (mg/mL)*	
			LDV	SBV
1	Pure drug	--	0.008 ± 0.001	0.936 ± 0.07
2	Drug – β-CD inclusion complex	1:0.1	0.052 ± 0.02	1.714 ± 0.14
		1:0.2	0.097 ± 0.06	3.582 ± 0.22
		1:0.3	0.161 ± 0.03	4.127 ± 0.19
3	Drug – Dimethyl β-CD inclusion complex	1:0.05	0.115 ± 0.04	6.263 ± 0.51
		1:0.1	0.161 ± 0.02	9.439 ± 0.43
		1:0.2	0.247 ± 0.07	10.914 ± 0.82
	Drug – HP β-CD inclusion complex	1:0.05	0.134 ± 0.03	4.725 ± 0.36
		1:0.1	0.189 ± 0.04	8.118 ± 0.27
		1:0.2	0.216 ± 0.02	10.692 ± 0.74

higher amount of CDs that would entrap more guest drug molecules and eventually resulted in increased solubility.[22]

The LSICs with dimethyl-β-CD and HP-β-CD at 1:0.2 ratios were considered as optimized because both these CDs exhibited almost similar solubilities. Hence, these LSICs and pure drug mixture were subjected to PXRD studies and the resultant spectra were shown in Figure 1. The spectrum of pure drugs exhibited more sharp peaks with high intensity indicating the crystalline state of the drugs. Whereas the spectra of the LSICs prepared with both the CDs showed more peaks with decreased intensity. This might be because of the conversion of the crystalline drug into amorphous form upon entrapment into the CD cavities followed by solidification after evaporation of the solvent.[23] This conversion into amorphous form could be the reason behind the increase in solubility of LDV and SBV.

These optimized complexes were subjected to flowability studies like angle of repose and Carr's index. The angle of repose values were found to be 16.2° and 14.9°; and the Carr's index values were found to be 13.1% and 12.7% respectively for the LSICs with dimethyl-β-CD and HP-β-CD. These results indicated that the LSICs had good flowability. But a further increase would be better during tablet compression. Hence, the LSICs were mixed with 1% glidant and then the flow properties were studied. Then, the values of angle of repose were found to be decreased to 13.8° and 12.6°; and the Carr's index values were found to be 12.4% and 12.2% respectively for the LSICs with dimethyl-β-CD and HP-β-CD. These high flowability and compressibility could be due to the aggregated form of the obtained LSICs upon solvent evaporation under vacuum evaporation. These

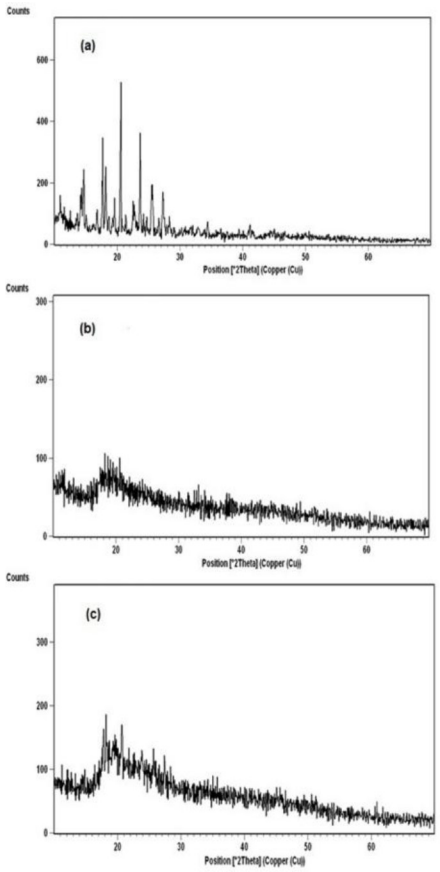

Figure 1: Powder X-ray diffraction spectra of a) Mixture of pure LDV and SBV b) Inclusion complexes of LDV and SBV with dimethyl-β-CD c) Inclusion complexes of LDV and SBV with HP-β-CD.

results indicated that suitability of the LSICs for direct compression into tablets.

Characterization studies of the FDTs

Physical characterization tests

The FDTs of all the formulations prepared from the optimized LSICs showed uniform weight in the range of 943 – 955 mg. The results of various characterization tests were shown in the Table 4. The friability of all the formulations were found to be in the range of 0.18 – 0.41%. These results were below the USP limit of 1% indicating the FDTs were passed the friability test.[24] The results of the tensile strength values were found to be in the range of 0.79 – 0.91 N/mm^2. These high tensile strength values could be attributed to the high degree of compressibility of the formulation compositions.[25] The friability and tensile strength results combinely indicated that the LSICs with minimum amount of MCC, the direct compressible vehicle was suitable for direct compression technique to get the tablets. Hence, it could be evident form these results that direct compression can be possible for high dose

Table 4: Results (Avg. ± S.D for *n* = 3) of physical characterization studies on ODTs of formulations F1 – F18.

Formulation	Tensile strength (N/mm^2)	Packing fraction (P_f)	Porosity fraction ($1 - P_f$)	Friability (%)	Wetting time (sec)	Disintegration time (sec)	Drug content (%)	
							LDV	SBV
F1	0.81 ± 0.05	0.84 ± 0.02	0.16 ± 0.02	0.36 ± 0.04	33.8 ± 2.7	106 ± 9	99.2 ± 2.4	101.4 ± 1.8
F2	0.85 ± 0.03	0.87 ± 0.05	0.13 ± 0.05	0.41 ± 0.06	24.7 ± 3.1	85 ± 7	98.7 ± 1.9	98.5 ± 2.4
F3	0.84 ± 0.02	0.82 ± 0.09	0.18 ± 0.09	0.28 ± 0.03	26.1 ± 2.9	73 ± 4	99.1 ± 2.1	100.2 ± 3.2
F4	0.89 ± 0.04	0.89 ± 0.03	0.11 ± 0.03	0.35 ± 0.04	40.7 ± 3.6	124 ± 11	101.3 ± 1.6	99.7 ± 1.6
F5	0.78 ± 0.01	0.85 ± 0.05	0.15 ± 0.05	0.22 ± 0.05	35.7 ± 4.5	90 ± 8	98.4 ± 3.2	99.3 ± 1.9
F6	0.86 ± 0.03	0.84 ± 0.06	0.16 ± 0.06	0.18 ± 0.07	32.4 ± 3.2	86 ± 6	99.5 ± 2.7	100.8 ± 2.4
F7	0.88 ± 0.02	0.81 ± 0.08	0.19 ± 0.08	0.39 ± 0.06	61.9 ± 5.8	145 ± 12	100.7 ± 3.6	98.5 ± 1.3
F8	0.82 ± 0.07	0.83 ± 0.09	0.17 ± 0.09	0.27 ± 0.04	52.3 ± 2.3	116 ± 13	98.9 ± 1.8	99.1 ± 3.2
F9	0.79 ± 0.04	0.83 ± 0.04	0.17 ± 0.04	0.25 ± 0.04	40.5 ± 3.1	122 ± 9	99.6 ± 2.5	98.9 ± 1.6
F10	0.89 ± 0.03	0.86 ± 0.08	0.14 ± 0.08	0.46 ± 0.08	27.6 ± 4.6	109 ± 10	100.3 ± 1.4	99.8 ± 2.8
F11	0.83 ± 0.06	0.82 ± 0.07	0.18 ± 0.07	0.33 ± 0.05	29.3 ± 5.2	81 ± 5	97.9 ± 2.2	98.4 ± 2.5
F12	0.84 ± 0.02	0.83 ± 0.05	0.17 ± 0.05	0.42 ± 0.03	25.3 ± 1.9	68 ± 4	98.5 ± 1.7	99.6 ± 3.4
F13	0.78 ± 0.03	0.88 ± 0.03	0.12 ± 0.03	0.27 ± 0.02	42.6 ± 3.5	102 ± 9	99.4 ± 3.1	100.2 ± 2.6
F14	0.81 ± 0.05	0.83 ± 0.04	0.17 ± 0.04	0.28 ± 0.04	25.7 ± 2.9	83 ± 7	99.6 ± 2.9	101.5 ± 1.5
F15	0.79 ± 0.06	0.85 ± 0.06	0.15 ± 0.06	0.36 ± 0.05	22.4 ± 2.6	75 ± 6	98.7 ± 2.6	97.8 ± 2.2
F16	0.88 ± 0.07	0.86 ± 0.02	0.14 ± 0.02	0.19 ± 0.03	41.9 ± 3.7	133 ± 11	101.6 ± 1.8	100.9 ± 3.1
F17	0.83 ± 0.08	0.89 ± 0.05	0.11 ± 0.05	0.21 ± 0.04	48.3 ± 5.4	124 ± 10	100.5 ± 2.7	99.4 ± 2.9
F18	0.91 ± 0.05	0.88 ± 0.04	0.12 ± 0.04	0.38 ± 0.05	30.5 ± 4.1	105 ± 12	99.1 ± 2.3	98.9 ± 1.4

drugs after suitable physical modification by solvent evaporation. During solvent evaporation, the material becomes perforated resulting in high porosity which can increase the tablet ability of the material.[26] Hence, even considerably high amount of 950 mg of the powder mixture with minimum amount of MCC was compressed effectively into tablets with good strength.

The packing fraction indicates how effectively the powder mixture was compressed to give a tablet of enough strength. These values were obtained in the range of 0.81 – 0.89 for all the formulations and were shown in the Table 4. These values indicated that the tablets were formed enough packageability to give desired strength to the tablets. The porosity of the compressed tablets is important to provide wicking action for penetration of water thereby promoting disintegration.[27] These values were obtained by subtracting the packing fraction from one and hence obtained in the range of 0.19 – 0.11 for the FDTs prepared. These values indicated that the FDTs had enough porosity for easy penetration of sufficient water. Hence, these results indicated that the FDTs prepared here had enough strength yet having desired porosity necessary for rapid disintegration.

Wetting Time

The results of wetting time were found to be in the range of 22.4 – 61.9 sec and were shown in the Table 4. These results were found to be influenced by both the type and concentration of superdisintegrants. Upon increase in the concentration of the superdisintegrant, the wetting time was found to be decreased. This might be because of the availability of more amount of the superdisintegrant that could absorb water quickly.[28] The order of efficiency of the superdisintegrants in terms of decreasing the wetting time was observed to be CP > CCS > SSG. This could be due to the specific surface area of the superdisintegrants which are 1.0, 0.82 and 0.24 m^2/g for CP, CCS and SSG respectively.[29-31] The higher the surface area available for a superdisintegrant, it can absorb more water rapidly and wet the tablet quickly to get ready for disintegration.[28]

Disintegration Time

The results of the disintegration time (DT – the Response 1) were shown in the Table 4. Influence of the formulation factors on the DT was Figure 2 (a) and 2 (b). The results indicated that the effect of type of CD on the DT was little but the FDTs having HP-β-CD showed better disintegration than the corresponding FDTs having dimethyl-β-CD. Upon increase in the concentration of the superdisintegrant, the DT was found to be decreased. This could be evident that more amount of water can be absorbed and high degree of swelling can happen at higher disintegrant concentrations that can result in rapid disintegration of the FDTs.[32] The type of the superdisintegrant used

also influenced the DT. The FDTs prepared with CP showed least DT values than the other formulations and the increasing efficiency for rapid disintegration was found to be in the order of SSG < CCS < CP. This could be attributed to the specific surface area of the superdisintegrant, which is highest for CP among the three.[29-31] Higher surface area of a superdisintegrant can absorb more water readily and disintegrate the tablet rapidly. These results were correlated with the wetting time results and the disintegration time results reported by Srikar G *et al*.[9]

Dissolution Studies

The results of the dissolution data kinetics of all the 18 formulations of FDTs for both the LDV and SBV were shown in the Table 5 including the LDV-T90% (Response 2) and SBV-T90% (Response 3). The influences of the factors on the Responses 2 and 3 were shown in the Figure 2 (b), 2 (c), 2 (d), 2 (e) and 2 (f). These results indicated that the FDTs having dimethyl-β-CD showed higher dissolution rates than the corresponding FDTs having HP-β-CD. Even though the dimethyl-β-CD containing FDTs disintegrated rapidly than those containing HP-β-CD, the dissolution was rapid for the later FDTs. This could be because of the higher solubility of the dimethyl-β-CD than HP-β-CD,[21] that might cause those FDTs dissolve rapidly irrespective of the disintegration times and resulted in shorter T90% times. These results were correlated with those reported by Creteanu A *et al*.[33] The type of the superdisintegrant also influenced the dissolution rate and hence T90% times. The T90% values of the FDTs containing CP and those of the FDTs containing CCS were similar to each other and significantly lower than those containing SSG. This could be due to the solubility enhancing nature of the CP and CCS,[29-30,34] that could result in rapid dissolution and shorter T90% values. Whereas SSG has a tendency to develop jelling,[31] that might show lesser dissolution rate and higher T90% values than the corresponding FDTs prepared with CP and CCS. Further, in case of all the three superdisintegrants, the dissolution rates were increased and the T90% values were decreased for both the drugs upon increasing the superdisintegrant concentration. This could be attributed to the rapid disintegration followed by dissolution at higher disintegrant concentrations. The results were correlated with those reported by Mahrous GM *et al*.[35] and Tafere C *et al*.[36]

Design validation

The experiment of developing FDTs in the present research work was performed using miscellaneous

Table 5: Dissolution kinetics data for LDV and SBV from the ODTs of formulations F1 – F18.

Formulation	Ledipasvir					Sofosbuvir				
	Regression values		Dissolution rate constant (k, min^{-1})	T90% (min.)	T50% (min.)	Regression values		Dissolution rate constant (k, min^{-1})	T90% (min.)	T50% (min.)
	Zero-order	First-order				Zero-order	First-order			
F1	0.679	0.99	0.094	24.5	7.4	0.761	0.99	0.114	20.2	6.1
F2	0.691	0.994	0.106	21.8	6.6	0.704	0.974	0.124	18.5	5.6
F3	0.632	0.993	0.124	18.6	5.6	0.646	0.983	0.152	15.2	4.6
F4	0.766	0.992	0.108	21.3	6.4	0.682	0.995	0.132	17.4	5.2
F5	0.705	0.99	0.122	18.9	5.7	0.582	0.996	0.143	16.1	4.8
F6	0.563	0.997	0.134	17.2	5.2	0.556	0.986	0.158	14.6	4.4
F7	0.894	0.978	0.083	27.7	8.4	0.821	0.982	0.101	22.8	6.9
F8	0.783	0.979	0.113	20.4	6.2	0.691	0.993	0.123	18.7	5.6
F9	0.78	0.987	0.105	21.9	6.6	0.672	0.996	0.119	19.3	5.8
F10	0.799	0.973	0.095	24.3	7.3	0.812	0.991	0.103	22.4	6.8
F11	0.762	0.985	0.101	22.9	6.9	0.677	0.993	0.137	16.8	5.1
F12	0.674	0.976	0.127	18.1	5.4	0.68	0.986	0.132	17.5	5.3
F13	0.785	0.997	0.088	26.2	7.9	0.793	0.932	0.104	22.1	6.7
F14	0.751	0.986	0.102	22.5	6.8	0.742	0.97	0.122	18.9	5.7
F15	0.644	0.99	0.124	18.6	5.6	0.619	0.993	0.141	16.3	4.9
F16	0.918	0.982	0.074	31.2	9.4	0.878	0.985	0.091	25.4	7.6
F17	0.85	0.99	0.087	26.3	7.9	0.765	0.993	0.112	20.5	6.2
F18	0.745	0.997	0.097	23.6	7.1	0.76	0.989	0.106	21.8	6.6

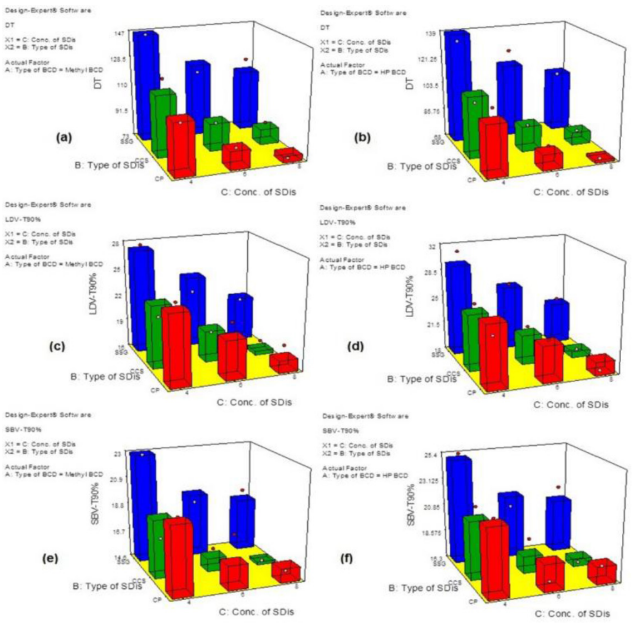

Figure 2: Influences of the factors on the responses a) Influence of the factors B and C on the response DT in case of the FDTs with dimethyl-β-CD Inclusion complexes b) Influence of the factors B and C on the response DT in case of the FDTs with HP-β-CD Inclusion complexes c) Influence of the factors B and C on the response LDV-T90% in case of the FDTs with dimethyl-β-CD Inclusion complexes d) Influence of the factors B and C on the response LDV-T90% in case of the FDTs with HP-β-CD Inclusion complexes e) Influence of the factors B and C on the response SBV-T90% in case of the FDTs with dimethyl-β-CD Inclusion complexes f) Influence of the factors B and C on the response SBV-T90% in case of the FDTs with HP-β-CD Inclusion complexes.

factorial design. Influence of the selected factors on the obtained response values were studied by a linear model. The influence of the factors on every response and the selected linear model were evaluated for their significance using ANOVA test,[17] and the results were shown in the Table 6. The selected linear model in case of all the three responses was found to be significant at $p < 0.05$, and the influences of all the three factors on every response were found to be significant at $p < 0.05$. The adjusted and predicted R^2 values respectively were found to be 0.9291 and 0.8874 for the DT; 0.8699 and 0.7934 for the LDV-T90%; and 0.8382 and 0.7431 for the SBV-T90%. The differences between the adjusted and predicted R^2 values were found to be below 0.2 for all the three responses. Hence, this indicated the design can be navigated for optimization. Further, the normal plot of residuals for all the three responses were show in Figure 3. These plots indicated that the response values scattered to form a straight line rather than sigmoid shape. This indicated that the selected design was suitable and could be navigated to further optimization.

Optimization

Numerical optimization by desirability functions approach was performed with the aid of the Design Expert software. The desirability criterion for the optimization was set as minimizing all the three responses DT, LDV-T90% and SBV-T90% towards the

Table 6: ANOVA test results for the three response variables.

Sl. No.	Response	Source	SS[a]	Df[b]	MSS[c]	*F* value	*p*-Value	Inference[d]
1	R1 – DT	Model	8227.06	5	1645.41	45.55	< 0.0001	*Significant*
		A: Type of β-CD	249.39	1	249.39	6.90	0.0221	*Significant*
		B: Type of SDis.	4744.33	2	2372.17	65.67	< 0.0001	*Significant*
		C: Conc. Of SDis.	3233.33	2	1616.67	44.76	< 0.0001	*Significant*
		Residual	433.44	12	36.12			
		Cor Total	8660.50	17				
2	R2 – LDV-T90%	Model	215.18	5	43.04	23.73	< 0.0001	*Significant*
		A: Type of β-CD	25.44	1	25.44	14.03	0.0028	*Significant*
		B: Type of SDis.	64.67	2	32.33	17.83	0.0003	*Significant*
		C: Conc. Of SDis.	125.07	2	62.54	34.49	< 0.0001	*Significant*
		Residual	21.76	12	1.81			
		Cor Total	236.94	17				
3	R3 – SBV-T90%	Model	130.52	5	26.10	18.62	< 0.0001	*Significant*
		A: Type of β-CD	19.84	1	19.84	14.15	0.0027	*Significant*
		B: Type of SDis.	48.95	2	24.47	17.45	0.0003	*Significant*
		C: Conc. Of SDis.	61.72	2	30.86	22.01	< 0.0001	*Significant*
		Residual	16.83	12	1.40			
		Cor Total	147.34	17				

Note: [a]-Sum of Squares; [b]-Degrees of Freedom; [c]-Mean Sum of Squares; [d]-p-Value less than 0.05 indicates model terms are significant

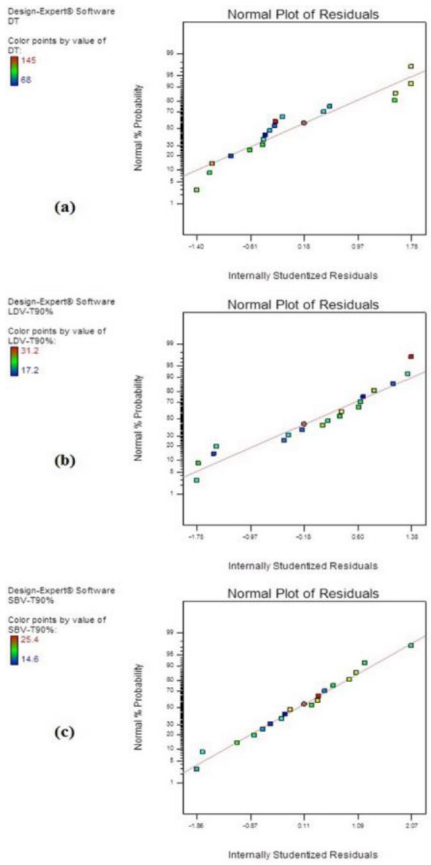

Figure 3: Normal plots of the residuals for the responses a) Disintegration time b) LDV-T90% c) SBV-T90%.

objective of increasing dissolution of both the drugs. Upon optimization, several combinations towards the optimization were suggested by the software. Among them, a combination with the maximum desirability of 0.92 was chosen,[17] with dimethyl-β-CD as the factor A, CCs as the factor B and 8% w/w of CCS as the factor C. At this combination the predicted values of the responses with 95% confidence intervals (CI) were shown in the Table 7. At this suggested optimized combination, again new FDTs was developed and subjected to disintegration and dissolution tests. The results of the DT and the LDV-T90% and SBV-T90% (shown in Table 7) were correlated and were within the 95% confidence intervals with the predicted values. These results confirmed the development of FDTs for the LDV and SBV combination with minimum disintegration time and rapid dissolution.

Further, the dissolution profile of this optimized FDT was compared with that of the marketed formulation (Ledifos Tablets) and was shown in the Figure 4. The time for the dissolution of 90% of LDV were 17.73 and 31.65 min. and of SBV were 13.68 and 24.51 min. respectively from the optimized FDTs and the

Table 7: Comparison of the predicted and observed values of the responses for the optimized formulation.

Factors combination	Responses	Predicted values	95% CI low	95% CI high	Observed values
A: Type of β-CD (Methyl β-CD)	R1: DT (sec.)	83.72	76.16	91.28	79.6
B: Type of SDis. (CCS)	R2: LDV-T90% (min.)	16.46	14.76	18.15	17.72
C: Conc. Of SDis. (8% w/w)	R3: SBV-T90% (min.)	14.83	13.34	16.32	13.68

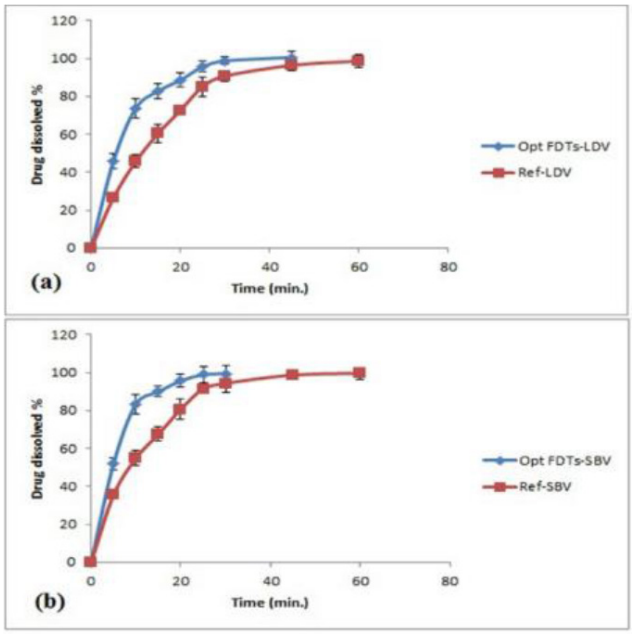

Figure 4: Comparative dissolution profiles of the optimized FDTs and the marketed tablets for a) Ledipasvir b) Sofosbuvir.

marketed formulation. These results indicated that a novel formulation of FDTs with rapid disintegration and dissolution better than the marketed formulation for the combination of LDV and SBV was successfully developed using statistical DoE.

CONCLUSION

The newly approved fixed dose combination drugs for the treatment of hepatitis-C, LDV and SBV were suffered with the drawback of dissolution limited oral bioavailability due to their poor water solubility. In the current research work, FDTs were aimed to develop for this combination drugs in order to improve their

dissolution thereby bioavailability. Inclusion complexes by solvent evaporation method using cyclodextrins were developed to improve the solubility of the drugs as well as the compressibility for developing them into direct compressible tablets. The experiment was performed employing statistical DoE using Design Expert software. Type of CD, type of superdisintegrant and concentration of superdisintegrant were taken as the independent factors and DT, LDV-T90% and SBV-T90% were taken as the responses. All the three responses were found to be significantly influenced by all the factors at $p < 0.05$. Numerical optimization was performed with the desirability of minimizing all the responses. The final optimized FDT formulation was identified as the one with dimethyl-β-CD as the complexing agent, CCS as the disintegrant at 8% w/w. This optimized FDT was found to have DT of 79.6 sec, LDV-T 90% of 17.72 min. and SBV-T90% of 13.68 min. These results indicated that optimized FDT was developed for the LDV and SBV with enhanced dissolution successfully using statistical DoE and the set objective of the present work was achieved.

ACKNOWLEDGEMENT

The authors are acknowledged to the authority of Jawaharlal Nehru Technological University-Kakinada (JNTUK), Kakinada for providing the opportunity to carry out this work and the management of Aditya College of Pharmacy for providing the facilities to carry out this work.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

ANOVA: Analysis of variance; **CCS:** Croscarmellose sodium; **CDs:** Cyclodextrins; **CI:** Confidence intervals; **CP:** Crospovidone; **Dimethyl-β-CD:** Dimethyl-β-cyclodextrin; **DMSO:** Dimethyl sulfoxide; **DoE:** Design of experiments; **DT:** Disintegration time; **FDTs:** Fast dissolving tablets; **HP-β-CD:** Hydroxypropyl-β-cyclodextrin; **LDV:** Ledipasvir; **LSICs:** Ledipasvir-Sofosbuvir inclusion complexes; **LS-FDTs:** Ledipasvir-Sofosbuvir fast dissolving tablets; **MCC:** Microcrystalline cellulose; **P_f:** Packing fraction; **PVP:** Povidone; **PXRD:** Powder X-ray diffraction; **R^2:** Regression; **SBV:** Sofosbuvir; **SSG:** Sodium starch glycolate; **T 90:** Time for dissolution of 90% of dose; **USFDA:** United States Food Drug Administration; **USP:** United States Pharmacopoeia.

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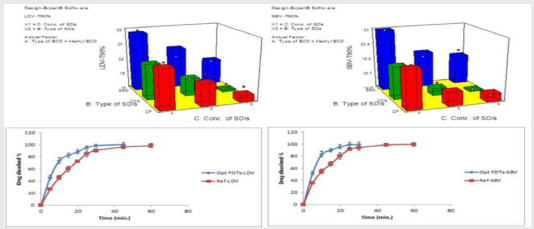
PICTORIAL ABSTRACT



SUMMARY

This research work was conducted to improve the dissolution limited bioavailability of Ledipasvir and Sofosbuvir by developing fast dissolving tablets for this drug combination. This was performed in two steps. Initially inclusion complexes were prepared using three different cyclodextrins. These were optimized for their solubility and identified that inclusion complexes with both HP-β-CD and Dimethyl-β-CD at 1:2 ratio provided maximum solubility for both the drugs. In the second step, fast dissolving tablets for these optimized inclusion complexes were developed by adopting DoE. Type of CD, type of superdisintegrant and concentration of superdisintegrant were taken as three independent factors for the selected 2x3x3 factorial design, and DT, LDV-T90% and SBV-T90% were taken as the responses. The prepared tablets were characterized for the responses and the obtained results were analyzed statistically using Design Expert software. All the three responses were found to be significantly influenced by all the three factors at $p < 0.05$. Further, numerical optimization revealed that the FDT with dimethyl-β-CD as the complexing agent, CCS as the disintegrant at 8% w/w as the optimized combination of the factors. The disintegration and dissolution test results of the final optimized FDTs were compared with those of the commercially available tablets. It was observed that the developed FDTs were found to have rapid disintegration and dissolution and hence the set objective of the work was achieved successfully.

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Cite this article: Thummala UK, Maddi EG, Avula PR. Optimization of Fast-dissolving Tablets of Ledipasvir-sofosbuvir Inclusion Complexes by Design of Experiments. Indian J of Pharmaceutical Education and Research. 2023;57(1):33-44.