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FORMULATION AND CHARACTERIZATION OF VELPATASVIR INSTANT RELEASE AND SOFOSBUVIR CONTROL RELEASE BILAYER TABLETS

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ABSTRACT

The formulation and characterization of bilayer tablets containing Sofosbuvir and Velpatasvir mark a significant advancement in pharmaceutical innovation aimed at improving hepatitis C treatment efficacy. This bilayer tablet design facilitates controlled and synergistic drug release, tailored to the distinct pharmacokinetic profiles of both active ingredients. Extensive optimization of pharmaceutical parameters including tablet thickness, hardness, friability, weight uniformity, and drug content was conducted to ensure the tablets' quality and uniformity. In-vitro dissolution studies revealed a well-defined release profile, showcasing differentiated release kinetics for Sofosbuvir and Velpatasvir across simulated physiological conditions. This formulation demonstrates robust pharmaceutical attributes, promising consistent quality and performance critical for enhancing therapeutic outcomes in hepatitis C management.

Keywords: Bilayer tablet, Sofosbuvir, Velpatasvir, Hepatitis C treatment, Controlled release, Pharmacokinetic profiles, Formulation optimization, Pharmaceutical quality, *In-vitro* dissolution profiling.

INTRODUCTION

The development of bilayer tablets represents a significant advancement in pharmaceutical drug delivery systems, particularly for combination therapies where different release profiles are desired. This approach facilitates the simultaneous administration of multiple drugs with distinct release characteristics, enhancing therapeutic efficacy and patient adherence. Bilayer tablets, which incorporate an instant release layer and a controlled release layer, offer a strategic advantage in managing chronic conditions and optimizing drug delivery.

Velpatasvir and Sofosbuvir are two potent antiviral agents used in the treatment of hepatitis C virus (HCV) infections. Velpatasvir is an NS5A inhibitor that disrupts the viral replication process, while Sofosbuvir is an NS5B polymerase inhibitor that interferes with viral RNA synthesis. The combination of these drugs has proven highly effective in achieving sustained virologic response (SVR), leading to significant improvements in patient outcomes (Bourliere *et al.,* 2015; Afdhal *et al.,* 2014). This dual action is crucial for a comprehensive treatment regimen, and integrating both drugs into a single bilayer tablet can enhance treatment adherence and overall efficacy.

The design of a bilayer tablet featuring Velpatasvir in the instant release layer and Sofosbuvir in the controlled release layer offers several advantages. The instant release layer allows for the rapid onset of Velpatasvir, providing immediate therapeutic effects and quick relief. Conversely, the controlled release layer ensures a steady, prolonged

release of Sofosbuvir, maintaining therapeutic drug levels over an extended period. This combination can potentially reduce the frequency of dosing and improve patient compliance, addressing the common challenge of adherence in chronic disease management (Lemke *et al.,* 2014; Reddy *et al.,* 2019).

Characterizing these bilayer tablets involves evaluating several critical parameters. Physical properties such as tablet hardness, friability, and dissolution rates are assessed to ensure the tablets meet mechanical and release criteria. Dissolution testing is particularly important to verify that Velpatasvir is released promptly while Sofosbuvir provides a controlled release over time. Additionally, chemical stability studies are conducted to confirm that both drugs retain their efficacy throughout the shelf life of the product. Drug content uniformity is also verified to ensure that each tablet contains the correct dosage of active ingredients, crucial for achieving consistent therapeutic outcomes (Jensen *et al.,* 2016; Khan *et al.,* 2015).

The aim of this research is to develop and characterize a bilayer tablet formulation that combines Velpatasvir, an NS5A inhibitor, and Sofosbuvir, an NS5B polymerase inhibitor, for the treatment of hepatitis C. Specifically.

MATERIALS AND METHODS

Preparation of bilayer tablet

Direct compression was used for preparation of the immediate release layer and wet granulation technology was used for Sustained release layer containing baclofen. For both the layer, granulation was carried out separately, as follows:

Preparation of immediate release layer (IR)

Velpatasvir immediate release tablets were prepared by direct compression method. Sift the lactose, cross carmellose sodium, avicel (pH-102), talc through #30 mesh, mixed and triturate with different surfactant such as poloxamer 188, sodium Stearate, sodium Lauryl sulfate. Again it all blended with Velpatasvir. Finally, this material passes through #30 mes (Goud, 2024).

Preparation of sustained release layer (SR)

It was performed by wet granulation method. In the wet granulation technique, 40 mg of Sofosbuvir and add each of the polymers (HPMC K4M and HPMC K100M) were granulated with Polivinyl pyrolidone (Binder). Granulates were passed through an 18-mesh screen and dried at 40°C for 2 hours. The dried granulate was mixed with other formulation components Micro crystalline cellulose (Diluent), 1.6 mg Magnesium stearate and Talc. Then compressed into flat tablets of 12 mm diameter (Makwana *et al.,* 2015).

Final compression of bilayer tablets

Bilayer tablets were prepared by feeding 150mg of SR granules manually into punch and compressed them with pre compression force. Then 650mg of IR granules were manually fed into same die cavity SR granules and applied final compression force into rotary tablet punching machine.

Evaluation of post compression parameters for bilayer tablets

Optimized formulation of Instant layer (IR6**)** and control layer (SR3) was used to prepare Bilayer tablets. Prepared immediate release tablets ware evaluated for post compression parameters like thickness and diameter,

hardness, friability, drug content, weight variation, and *In-vitro* drug release study.

Thickness and diameter

Thickness and diameter of tablets were accurately measured by using digital Vernier caliper for desired uniformity in size and shape.

Hardness

Tablet requires certain amount of strength or hardness which was measured by Monsanto hardness tester (Lachman *et al.,* 2004). Ten tablets were randomly picked from each formulation and were subjected for relative hardness and the value was expressed in Kg/cm^2.

Friability

The tablets were subjected to the test of friability with initial weight (Wi) almost equivalent to 6.5g of the tablets. The tablets were allowed to fall on it from a height of 6 inches while the friabilator drum was rotated at 25rpm for 4 minutes. The final weight (Wf) of the tablets after subjecting to friability was noted and the friability was calculated according to the formula (USP; 2004).

Friability (%) = (initial weight–final weight)/initial weight*100

Drug content

20 tablets were accurately weighed and powdered. Then powder equivalent to 10 mg of each drug was shaken vigorously with 50 ml of 0.1 N hydrochloric acid for 10 min and added sufficient 0.1 N hydrochloric acid to produce 100 ml and filtered. Each ml of filtrate was suitably diluted to 10 ml distilled water. The absorbance of resulting solution was measured at 301nm and 264 nm. Concentration of both the drug was calculated by simultaneous equation method using formula (Kamble *et al.,* 2018).

$$C_{VAL} = \frac{A_1 a y_2 - A_2 a y_2}{a x_1 a y_2 - a x_2 a y_1} \quad \ldots\ldots\ldots\ldots\ldots \text{Eq. (1)}$$

$$C_{SBL} = \frac{A_1 a x_2 - A_2 a x_1}{a x_1 a y_2 - a x_2 a y_1} \quad \ldots\ldots\ldots\ldots\ldots \text{Eq. (2)}$$

Weight variation

Twenty tablets were selected randomly and weighed individually. Average weight was calculated and compared the individual tablet weight to the average weight (Sudhakar *et al.,* 2019).

***In-vitro* drug release study of bilayer tablet**

USP apparatus II was used to test the dissolution profile using 900 ml of 0.1N HCl as dissolution medium at 50 rpm and 37◦C ± 0.5°C. six tablets from each batch were placed into respective basket containing HCl. 10ml of the sample was withdrawn hourly for 8h. The sample was filtered and from the filtrate 3ml was withdrawn. The volume was adjusted to 100ml with 0.1N HCl in the 100 ml to prepare 10 mcg/ml solutions. Absorbance of the solution was measured using UV spectrophotometer by simultaneous equation method (Lachmann; 1990).

Dissolution Conditions:

Medium:	0. 1N HCl
Type of Apparatus: (paddle type)	USP –XXIV
RPM:	75
Volume:	900 mL
Run time:	1hour
Temperature:	37± 0.5^{0}C

Kinetics of *in-vitro* drug release

For this study among all the batches A5, A6 and A9 from HPMC K4M group and C2, C3, and C4 from HPMC K4M and NaCMC combination group was selected. To study the release kinetics of In-vitro drug release data of above selected batches were applied to kinetic models.

RESULTS AND DISCUSSION

The formulation and evaluation of instant release (IR) and sustained release (SR) tablets, as well as bilayer tablets containing Velpatasvir and Sofosbuvir, were systematically investigated to optimize drug delivery for hepatitis C treatment.

Table 4 and Table 5 present the pre-compression evaluation parameters of the IR and SR batches, respectively. For the IR tablets, the angle of repose ranged from 25.4° to 29.8°, indicating good flowability of the powders used in the formulation. The bulk and tapped densities, along with the Carr index and Hausner ratio, suggest that the powders exhibit moderate to good compressibility and flow properties. The Carr index values for the IR batches ranged from 29.33% to 32.30%, and Hausner ratios varied from 1.415 to 1.477, indicating fair flowability and compressibility. Similarly, for the SR tablets, angles of repose were slightly higher, ranging from 24.47° to 28.95°, suggesting that the SR formulations had better flow properties compared to IR batches. The bulk densities ranged from 0.321 gm/ml to 0.365 gm/ml, and tapped densities from 0.452 gm/ml to 0.487 gm/ml, with Carr index values between 23.67% and 28.98% and Hausner ratios ranging from 1.310 to 1.395. These results indicate that the SR powders were slightly less compressible but still suitable for tablet formulation.

Tables 6 and 7 outline the post-compression characteristics of the IR and SR tablets, respectively. For the IR tablets, parameters such as weight variation, thickness, hardness, friability, disintegration time, and drug content were well within acceptable limits. The average weight of IR tablets ranged from 147 mg to 155 mg, thickness from 2.12 mm to 2.32 mm, and hardness from 2.6 kg/cm² to 2.9 kg/cm². The friability values ranged from 0.45% to 0.77%, indicating good tablet durability. The disintegration times were between 26 seconds and 42 seconds, which is consistent with the intended rapid release of the active drug. Drug content for IR tablets was between 95.85% and 99.12%, reflecting good uniformity of drug distribution.

In the case of SR tablets, average weights ranged from 452 mg to 458 mg, with thickness from 3.22 mm to 3.62 mm and hardness from 5.6 kg/cm² to 5.8 kg/cm². The friability values ranged from 0.32% to 0.85%, suggesting satisfactory tablet integrity. Drug content was consistent, ranging from 96.37% to 99.85%. These results highlight the successful formulation of SR tablets with appropriate characteristics for sustained drug release.

The dissolution profiles presented in Tables 8 and 9 demonstrate the release kinetics of the IR and SR tablets. For the IR tablets, the drug release rates showed rapid dissolution, with over 70% of the drug released within 30 minutes. Specifically, at 10 minutes, the release varied from 23.32% to 55.45%, and by 30 minutes, it ranged from 70.12% to 98.85%. This rapid release profile is indicative of the effectiveness of the instant release layer in providing quick therapeutic action.

Conversely, the SR tablets displayed a controlled release pattern. The initial release was slow, with only 18.58% to 26.54% drug released after 1 hour. By 12 hours, the release varied from 91.12% to 99.45%, reflecting a sustained release profile that maintains therapeutic levels over an extended period. This extended release is crucial for

maintaining effective drug concentrations and improving patient compliance.

Table 10 shows the post-compression parameters of the optimized bilayer tablets. The tablets exhibited a thickness of 3.85 mm, hardness of 5.75 kg/cm², and a friability of 0.745%, indicating good mechanical properties. The weight variation was 655 mg, and the drug content for Velpatasvir and Sofosbuvir was 99.85% and 99.45%, respectively, confirming uniform drug distribution.

Table 11 provides the in-vitro dissolution profile of the bilayer tablets. Velpatasvir released 86.65% after 15 minutes and reached 98.85% after 12 hours, while Sofosbuvir showed a slower release profile, starting with 5.85% after 15 minutes and reaching 91.12% at 12 hours. This profile supports the effectiveness of the bilayer design, with Velpatasvir providing rapid release and Sofosbuvir offering sustained release.

Table 1: Formulation of immediate release layer of Velpatasvir

Ingredients (mg)	**Qty. (mg/tab)**					
	IR1	**IR2**	**IR3**	**IR4**	**IR5**	**IR6**
Velpatasvir	100	100	100	100	100	100
MCC PH102	46	44	42	46	44	42
Sodium starch Glycolate	2	4	6	-	-	-
Croscarmellose sodium	-	-	-	2	4	6
Magnesium stearate	1	1	1	1	1	1
Talc	1	1	1	1	1	1
Total weight	150	150	150	150	150	150

Table 2: Formulation of immediate release layer of Sofosbuvir

Ingredients (mg)	**Qty. (mg/tab)**					
	SR1	**SR2**	**SR3**	**SR4**	**SR5**	**IR5**
Sofosbuvir	400	400	400	400	400	400
HPC K4M	30	40	50	-	-	-
HPMC K100M	-	-	-	30	40	50
PVP K 30	10	10	10	10	10	10
Dicalcium Phosphate	56	46	38	58	48	38
Magnesium stearate	2	2	1	1	1	1
Talc	2	2	1	1	1	1
IPA	qs	qs	qs	qs	qs	qs
Total weight	500	500	500	500	500	500

Table 3: Evaluation Parameters of Optimized Formulation

Ingredients (mg)	Qty. (mg)
Velpatasvir	100
MCC PH102	42
Sodium starch Glycolate	-
Croscarmellose sodium	6
Magnesium stearate	1
Talc	1
	150
Sofosbuvir	400
HPC K4M	50
HPMC K100M	-
PVP K 30	10
Dicalcium Phosphate	38
Magnesium stearate	1
Talc	1
IPA	qs
	500
Total = 650 mg	

Table 4: Pre-compression Evaluations of Batches IR1 to IR6

F. Code	Angle of repose (Degree)	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr index	Hausner ratio
IR1	28.5±0.2	0.245±0.012	0.348±0.021	29.598±0.023	1.420±0.015
IR2	29.8±0.1	0.265±0.015	0.375±0.032	29.333±0.015	1.415±0.022
IR3	26.7±0.3	0.236±0.023	0.348±0.014	32.184±0.022	1.475±0.014
IR4	25.4±0.2	0.241±0.014	0.356±0.056	32.303±0.012	1.477±0.012
IR5	27.7±0.1	0.255±0.023	0.362±0.014	29.558±0.014	1.420±0.011
IR6	26.6±0.2	0.263±0.011	0.374±0.032	29.679±0.013	1.422±0.13

Table 5: Pre-compression Evaluations of Batches SR1 to SR6

F. Code	Angle of repose (Degree)	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr index	Hausner ratio
SR1	27.85±0.25	0.321±0.023	0.452±0.012	28.982±0.015	1.408±0.032
SR2	28.95±0.32	0.352±0.015	0.469±0.014	24.947±0.023	1.332±0.012
SR3	27.74±0.14	0.365±0.032	0.487±0.023	25.051±0.014	1.334±0.014
SR4	26.65±0.35	0.341±0.014	0.465±0.015	26.667±0.026	1.364±0.025
SR5	24.47±0.21	0.332±0.033	0.463±0.022	28.294±0.041	1.395±0.032
SR6	28.85±0.41	0.345±0.015	0.452±0.032	23.673±0.036	1.310±0.015

Table 6: Post-compression Evaluations of Batches IR1 to IR6

F. Code	Weight variation	Thickness (mm)	Hardness (kg/cm^2)	% Friability	Disintegration time (sec)	% Drug Content
IR1	148±3	2.15±0.02	2.9±0.2	0.74±0.03	42±4	96.65±0.21
IR2	155±2	2.22±0.03	2.8±0.4	0.56±0.05	38±2	98.85±0.36
IR3	147±4	2.32±0.06	2.6±0.5	0.63±0.02	32±5	97.12±0.45
IR4	149±3	2.14±0.04	2.8±0.2	0.45±0.03	38±4	95.85±0.21
IR5	152±2	2.12±0.02	2.8±0.1	0.65±0.02	35±3	96.63±0.25
IR6	147±4	2.21±0.04	2.7±03	0.77±0.01	26±2	99.12±0.32

Table 7: Post-compression Evaluations of Batches SR1 to SR6

F. Code	Average Weight (mg)	Thickness (mm)	Hardness (kg/cm^2)	% Friability	% Drug Content
SR1	452±6	3.62±0.05	5.8±0.5	0.65±0.06	98.45±0.25
SR2	458±5	3.45±0.07	5.6±0.7	0.45±0.05	97.74±0.32
SR3	452±4	3.52±0.08	5.7±0.9	0.32±0.04	99.85±0.15
SR4	456±8	3.22±0.09	5.8±0.4	0.74±0.03	96.65±0.36
SR5	457±5	3.45±0.06	5.6±0.3	0.55±0.02	97.42±0.21
SR6	453±4	3.36±0.04	5.8±0.4	0.85±0.04	96.37±0.24

Table 8: *In-vitro* drug release of batches IR1 to IR6

Time (Min)	IR1	IR2	IR3	IR4	IR5	IR6
5	23.32	25.65	29.98	36.65	45.65	55.45
10	30.12	34.74	32.12	48.85	59.98	69.98
15	38.85	40.15	53.32	60.55	68.85	76.65
20	56.65	66.85	72.23	73.25	76.65	89.98
25	63.32	67.74	80.13	81.74	82.12	93.58
30	70.12	73.12	85.65	88.85	89.98	98.85

Table 9: *In-vitro* drug release of batches SR1 to SR6

Time (Hrs)	SR1	SR2	SR3	SR4	SR5	SR6
1	18.58	23.32	24.56	26.54	22.43	11.23
2	22.32	29.98	32.45	29.25	30.54	18.64
3	26.65	34.45	38.34	38.66	35.87	28.45
4	36.65	38.85	45.23	84.87	45.65	34.26
6	42.25	46.65	70.26	51.28	54.16	52.47
8	59.98	63.32	88.82	83.89	63.38	69.78
10	63.32	69.98	92.32	98.16	85.49	87.69
12	75.65	78.84	99.45	-	91.12	92.43

Table 10: Results evaluation of post compression parameters for bilayer tablets

S. No.	Parameters	Results	
1.	Thickness	3.85±0.45	
2.	Hardness	5.75±0.25	
3.	Friability	0.745±0.32	
5.	Weight variation	655±0.18	
4.	Drug content	Velpatasvir	Sofosbuvir
		99.85±0.11	99.45±0.25

Table 11: *In vitro* Dissolution profile of optimized bilayer tablets

Time	Media	Velpatasvir	Sofosbuvir
15 min	0.1 N HCl	86.65	5.85
30 min		99.05	8.98
1 hr			13.36
2 hr			18.25
3 hr			26.65
4 hr			34.47
6 hr			53.23
8 hr			64.45
10 hr			85.45
12 hr			98.85

CONCLUSION

The development and characterization of the bilayer tablets containing Velpatasvir and Sofosbuvir demonstrate successful formulation with desirable release profiles for effective hepatitis C management. The IR tablets provide quick therapeutic action, while the SR tablets offer prolonged drug release, enhancing patient compliance and therapeutic efficacy. The optimized bilayer tablets effectively combine these attributes, providing a sophisticated solution to manage hepatitis C treatment more efficiently

DECLARATION OF INTEREST

The authors declare no conflicts of interests. The authors alone are responsible for the content and writing of this article.

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