RESEARCH PAPER

Formulation and Characterization of Sofosbuvir Microspheres Loaded Controlled Release Tablets

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ABSTRACT

Introduction: Sofosbuvir (SFBVR) is an antiviral drug with less stability in stomach pH, poor flow property and short transit time of 0.5 hrs insists to make a modified release dosage form. So, the present study aimed to formulate SFBVR microspheres (MSPs) in controlled release tablet dosage form.

Methods: SFBVR-MSPs were fabricated using emulsion solvent evaporation method in which hydroxyl propyl methyl cellulose (HPMC) acts as polymer-matrix around the MSP, enhances encapsulation efficiency (ECE), ethyl cellulose sustains the release, acetone to solubilize drug and polymer, tween 80 which controls the particle size and glycerin supports the formation of uniform size MSPs. The prepared formulations underwent analysis for morphological and physical properties.

Results: Fourier-transform infrared spectroscopy (FTIR) studies revealed no interaction between the drug and excipients. F3 exhibited highest percentage yield, ECE and drug release. Evaluated pre-compression studies proved the improved flow property of the six MSPs formulations. SEM images of the optimized formulation displayed uniform and spherical MSPs. To avoid the short transit time the F3 was formulated into controlled release tablets and evaluated for post compression parameters. SFBVR-MSPs loaded tablets released 95.76 % of drug in 12 hrs followed Higuchi kinetics, indicating diffusion-controlled release, with Korsmeyer–Peppas pattern suggesting a non-Fickian mechanism involving both diffusion and polymer relaxation.

Conclusion: SFBVR-MSPs loaded controlled release tablets are the propitious delivery system effective in the treatment of hepatitis, the constant release of drug for the prolonged dosing periods can impart promising patient compliance.
Keywords: *Sofosbuvir; Microspheres, Sustained release, Emulsion solvent evaporation*
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INTRODUCTION

Modified delivery systems are engineered to administer precise amounts of therapy directly to targeted areas for specific durations. This approach enhances treatment effectiveness while minimizing adverse effects [1]. Within pharmaceutical research and development, controlled drug delivery systems play a pivotal role, granting pharmaceutical molecules a renewed opportunity and providing temporal and/or spatial control over medication release pattern of the orally administered drugs [2, 3]. These dosage formulations ensure a relatively constant drug concentration at the site of action, prevent peak medication levels, reduce dosing frequency, mitigate adverse effects, and enhance patient compliance and therapeutic outcomes. In such systems, drug release commences upon administration, akin to traditional dosage forms.

SFBVR is a nucleotide analog inhibitor that used in Hepatitis C Virus (HCV) treatment with high cure rates and approved in over 100 countries, as monotherapy or in combination regimens. The primary patent for SFBVR expired in 2024, which open the gates for generic formulators with modified release dosage forms to overcome the reported limitations of SFBVR [4-8].

Comparing with the conventional dosage forms the MSPs loaded controlled release tablets believed to decrease intensity of adverse drug reactions, enhanced stability in GI tract, there by improves the therapeutic consistency.

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MSPs are the spherical particles of active drug molecule dispersed either in a molecular (non-granular) system or in large particles within a polymer matrix. Size of MSPs ranging from 1 to 1000 µm and can be in microcrystalline form, or present some form of drug-dispersion systems in certain solvents or solutions. The system of MSPs is suitable for SFBVR to get uniform particles and to increase flowability. The present study aimed to formulate SFBVR-MSPs for making controlled release dosage forms to over come the limitations associated with the conventional tablet dosage forms.

MATERIALS AND METHODS

MATERIALS

Chemicals

Sofosbuvir was a gifted sample from Viruj Pharmaceuticals, Hyderabad, India. All the excipients and solvents employed in the formulation of MSPs were purchased from Jay Chem Marketing Mumbai, India.

METHODS

1. Preparation and assessment of MSPss:

SFBVR-MSPs were formulated using the composition given Table 1. Drug and polymers were dissolved in acetone which works as dispersed phase then the mixture was loaded into a syringe, introduced drop wise into a continuous phase containing glycerin and tween 80 under stirring. A mechanical stirrer is employed to maintain constant agitation during the emulsification process. The mixing is continued for a specified duration, typically 1 hour, at a predetermined speed (1000 rpm), ensuring thorough dispersion of the drug-polymer solution within the continuous phase. During the emulsification process, the dispersed phase (drug-polymer solution) is emulsified into small droplets within the continuous phase (glycerin). As the solvent evaporates, solid microspheres containing the drug and polymers are formed.

Table 1: Composition of SFBVR-MSPs

Formulation	F1	F2	F3	F4	F5	F6
Drug (mg)	100	100	100	100	100	100
HPMC (mg)	100	150	200	100	150	100
EC (mg)	100	100	100	150	150	200
Acetone (ml)	20	20	20	20	20	20
Tween 80 (w/v)	0.5 %	0.5 %	0.5 %	0.5 %	0.5 %	0.5 %
Glycerin (ml)	100	100	100	100	100	100

Drug- sofosbuvir, EC- ethyl cellulose, HPMC– hydroxypropyl methyl cellulose

EVALUATION OF SFBVR-MSPS

1. Percentage yield

The SFBVR-MSPs were weighed after complete drying. Percentage yield values are tabulated in the results section [1].

$$\%\ \textbf{Yield} = \frac{\text{Weight of SFBVR} - \text{MSPsx100}}{\text{Total weight of solids}}$$

2. Encapsulation efficiency

MSPs equivalent to 10 mg of the drug were accurately weighed and dissolved in methanol or DMSO and volume made up to 100 mL in a volumetric flask. Further dilutions were done and absorbance was observed at wavelength 261 nm against blank under UV Spectrophotometer (LAB INDIA PVT LTD, Mumbai, India) and results were observed in triplicate [9].

$$\text{ECE} = \frac{\text{Actual drug content x100}}{\text{Theoretical drug content}}$$

3. Micromeritic properties:

Flow property of formulated SFBVR-MSPs were evaluated by measuring bulk density, tapped density, angle of repose, Carr's compressibility index, Hausner's ratio and the results were given in Table 3.

4. Fourier transform infrared spectroscopy (FTIR): FTIR (Bruker FTIR, Invinio, Japan) spectra were recorded for the fabricated formulations. Compatibility analysis was done for SFBVR-MSPs and the results were discussed in the results section.

5. Scanning electron microscopy (SEM)

SEM analysis is significant for the determination of surface texture and size of the particle. A SEM model JEOL JSM-5200 was utilized at acceleration potential of 15 KV and 30 KV at work distances (WD) 14 mm and 41 mm respectively, at different magnifications.

6. *In-vitro* dissolution studies for microspheres: 145 mg of MSPs equivalent to 100 mg of pure drug were taken for *in-vitro* analysis. 900 mL of the (pH 7.4) simulated intestinal medium was taken in a basket of USP dissolution test apparatus (model DS 8000) type 2 (paddle). Dialysis tubing cellulose membrane with an average flat width of 25 mm and soaked in pH 7.4 phosphate buffer for 24 hours. MSPs were taken into previously equilibrated membrane and the membrane's other end is tied with thread. Now it is placed in the basket. The temperature kept at 37±0.5℃, at 50 rpm. 5mL of the spent medium was replaced with fresh buffer to maintain sink conditions. Samples were withdrawn for 10 hours with a duration of 30 min. The collected samples were observed in the UV visible spectrophotometer at the wavelength of 261 nm where the drug is detected. Dilutions were done based on necessity.

The optimized MSPs were fabricated into tablet dosage form by direct compression with 120 mg microcrystalline

cellulose, 80 mg of lactose, 15 mg of crospovidone, 5 mg of magnesium stearate. Post compression, *in-vitro* drug release and pharmacokinetic behaviour of tablet were evaluated [10-13].

RESULTS AND DISCUSSION

1. Preparation and evaluation of SFBVR-MSPs

ECE of SFBVR-MSPs was within the range of 69.67-78.55 % (Table 2). Among all the formulations F3shows good ECE. Drug entrapment was greater in the F3 formulation at, HPMC:EC in 1:2 proportion. This can be attributed to the structural differences between types and solubility of polymer used in the formulation.

Table 2: Encapsulation efficiency of SFBVR-MSPs

Formulation	% Entrapment efficiency (%)
F1	72.54
F2	69.07
F3	78.84
F4	73.91
F5	70.82
F6	71.18

2. Assessment of micromeritic properties

Bulk density, tapped density, Carr's index, Hausner's ratio, angle of repose of F1-F6 SFBVR-MSPs were in the range of 0.545–0.562 g/cc, 0.653–0.658 g/cc, 10.04–13.92 % 1.14–1.18 and 24.13°–24.44° respectively, confirm that all formulations exhibited good to excellent flow properties (Table 3).

HPMC and EC diminished inter-particle attrition there by enhanced good flow through the even morphology of SFBVR-MSPs [14]. Aggregation between the MSPs was reduced due to hydrophobic nature of EC which in turn improved flow properties [15]. Tween 80 also played role in making the uniform MSPs to enhance the flow [16].

3. % Yield

The % yield graded from 76.41% to 81.63%, with F3 and F6 displaying better yields. This demonstrates, optimal ECE, less processing wastage and good preciseness of the process.

Table 3: Flow properties of SFBVR-MSPs

Formulation	Bulk density (gm/cc)	Tapped density (gm/cc)	Carr's index	%Yield	Hausner's ratio	Angle of repose
F1	0.545±0.58	0.654±0.32	11.01±0.12	76.41±0.25	1.18±0.42	24.13±0.32
F2	0.560±0.17	0.653±0.28	13.92±0.23	80.17±0.28	1.16±0.33	24.32±0.16
F3	0.562±0.26	0.658±0.16	10.04±0.52	81.63±0.44	1.18±0.40	24.43±0.35
F4	0.561±0.21	0.653±0.42	11.14±0.37	78.63±0.51	1.16±0.44	24.34±0.23
F5	0.562±0.38	0.655±0.22	12.87±0.33	80.22±0.45	1.14±0.15	24.44±0.18
F6	0.561±0.62	0.651±0.18	11.82±0.45	80.91±0.33	1.16±0.27	24.14±0.48

4. Drug-excipient compatibility studies

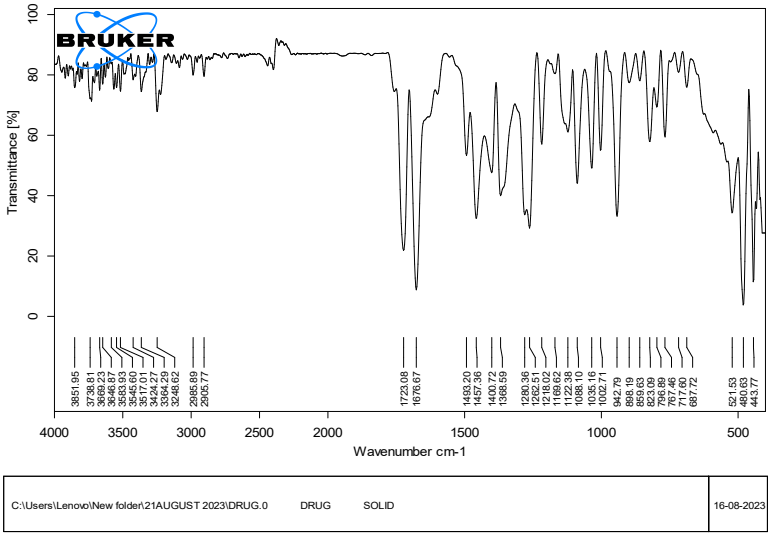

Figure 1: FTIR of SFBVR

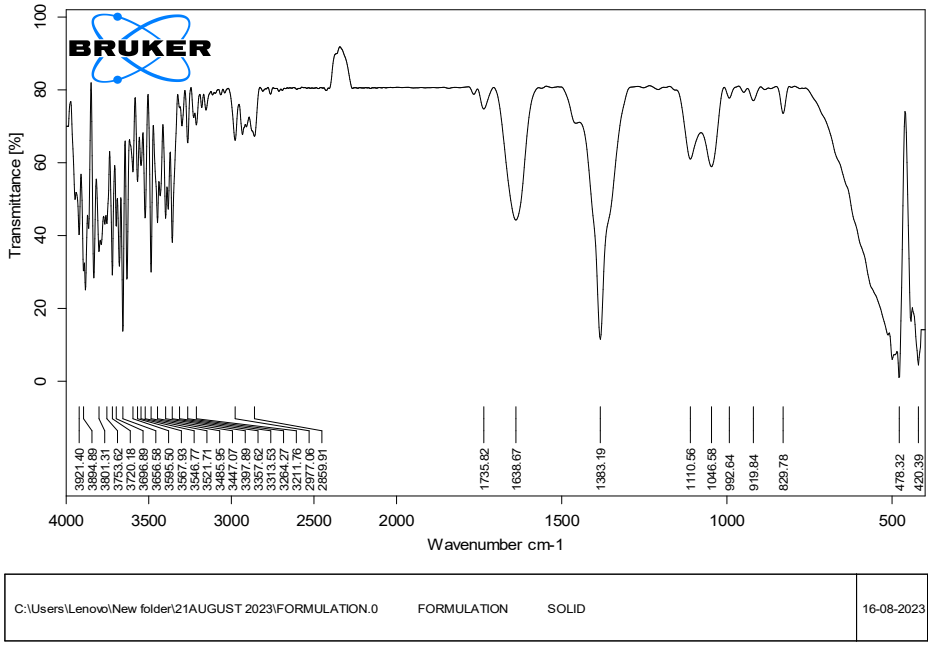

Figure 2: FTIR of SFBVR-MSPs

FTIR peaks shown in Fig 1 at 3353 cm^{-1} (N–H), 2978 cm^{-1} (C–H), 1721 cm^{-1} (C=O) were reported for SFBVR. C–O–C stretching bands in 1170–1000 cm^{-1} area are mark the pure SFBVR structure [17]. The optimized MSPs demonstrated all significant peaks of the drug with negligible changes and no new peak generation, stating the absence of chemical interaction between the drug and polymers as shown in Fig 2. These results confirm the compatibility and successful encapsulation of the drug within the microsphere system [18].

5. Microscopic imaging

The microscopic images of pure drug and MSPs were given in Figure 3A and 3B. As shown in the images, the shape of the pure drug is irregular and the MSPs have even shape. Emulsion solvent evaporation method used in the fabrication of MSPs has successfully achieved the uniform size of MSPs which in turn improve the flow property of the drug. The shape and size of the MSPs were further confirmed by SEM, found that the majority of the MSPs were in the size of 10 µm with spherical shape as shown in Fig 4.

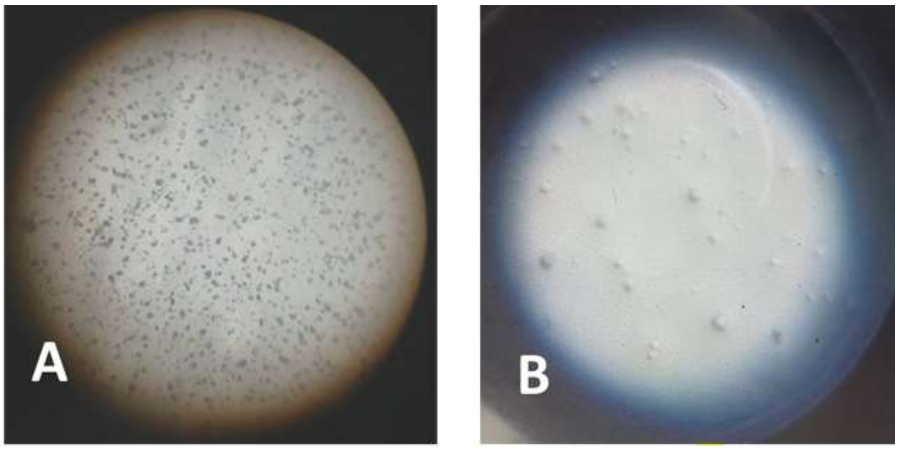

Figure 3: F3 Microscopic view of SFBVR and MSPs

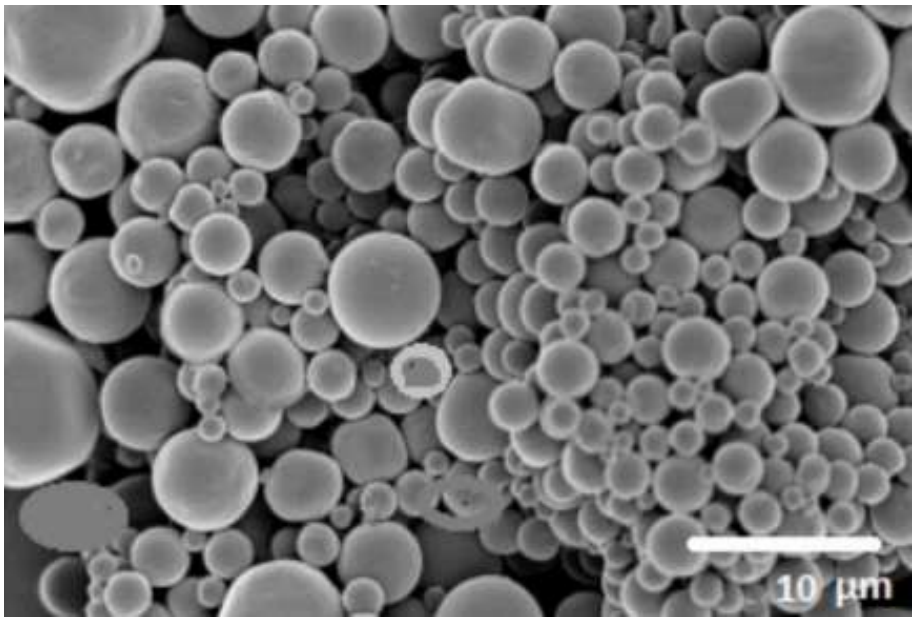

Figure 4: SEM photographs of SFBVR-MSPs

6. *In vitro* drug release of SFBVR-MSPs

Table 5 describes the drug release pattern of MSPs. After ten hours, more than 78 % of the medication was released from all of the microsphere formulations. The presence of a drug closer to the surface often determines release rate, and its presence reduces as polymer concentration increases and the amount of uncoated drug decreases. Higher polymer concentrations result in a denser polymer matrix, which lengthens the diffusion path and reduces total drug release from the polymer matrix. HPMC imparts higher release rate of drug from MSPs because of their high permeability and hydrophilic character [19-23]. This speeds up the release and expands the matrix's porosity. The drug release reduced from MSPs as the EC concentration in the formulation (F1,F2,F3,F4,F5,F6) rose. The microspheres that were made with SFV:HPMC:EC in a 1:2:1 (F3) ratio were found to release 90.45±0.1% of the total SFBVR in a satisfactory manner. F3 was used for preparation of controlled release tablets without adding the polymer that retards further release of drug. Evaluated post compression parameters for the prepared tablet dosage form were within the acceptable limits. 95.76 % of drug from the controlled tablet dosage form was released for about 12 hours, there is no further release of drug up to 12 hours.

Table 4: % Drug release of microspheres of F1-F6

Time(min)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
5	3.13±0.1	3.27±0.7	4.67±0.3	4.99±0.2	3.73±0.5	3.47±0.4
10	5.25±0.2	4.72±0.3	7.98±0.7	7.11±0.5	4.62±0.3	5.75±0.1
30	8.76±0.3	5.23±0.1	11.43±0.3	11.32±0.4	7.51±0.1	9.28±0.2
60	17.32±0.2	14.56±0.4	23.12±0.8	26.39±0.1	19.59±0.3	21.36±0.8
120	33.31±0.7	30.72±0.2	39.42±0.7	30.05±0.6	35.36±0.6	37.45±0.1
180	41.56±0.4	38.35±0.5	47.83±0.3	36.73±0.5	43.92±0.8	45.92±0.6
240	57.28±0.5	54.76±0.6	63.42±0.5	51.25±0.4	59.75±0.2	51.16±0.4
300	68.53±0.8	61.26±0.4	70.76±0.3	59.86±0.8	67.23±0.2	58.73±0.1
360	70.17±0.3	77.98±0.5	77.7±0.1	74.32±0.1	72.21±0.4	65.53±0.7
420	74.35±0.7	81.76±0.3	80.48±0.7	79.87±0.4	74.39±0.7	68.21±0.4
480	82.06±0.1	89.29±0.1	88.09±0.6	86.21±0.3	77.34±0.5	72.16±0.2
540	82.34±0.6	89.43±0.5	89.23±0.3	86.43±0.2	80.54±0.2	76.31±0.6
600	83.77±0.4	89.51±0.4	90.45±0.1	86.66±0.7	84.65±0.3	78.65±0.8

7. Release mechanisms of drug in graphical manner

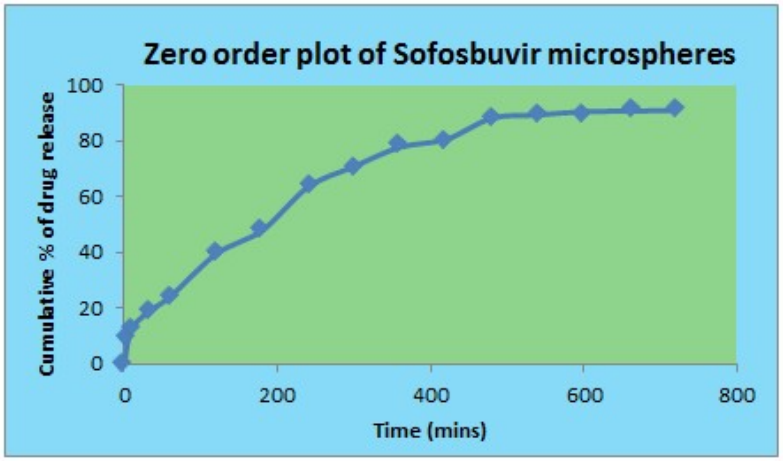

Figure 5: Zero order plot of Sofosbuvir microspheres

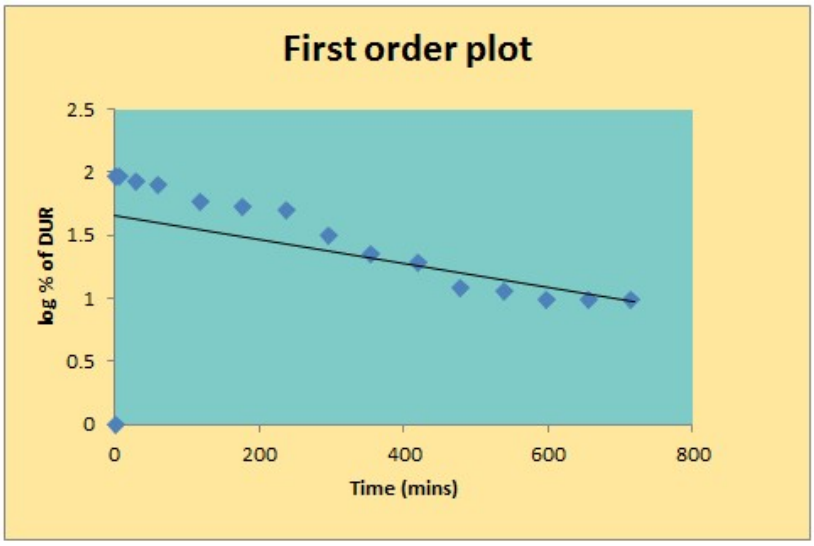

Figure 6: First order plot of sofosbuvir tablet formulation

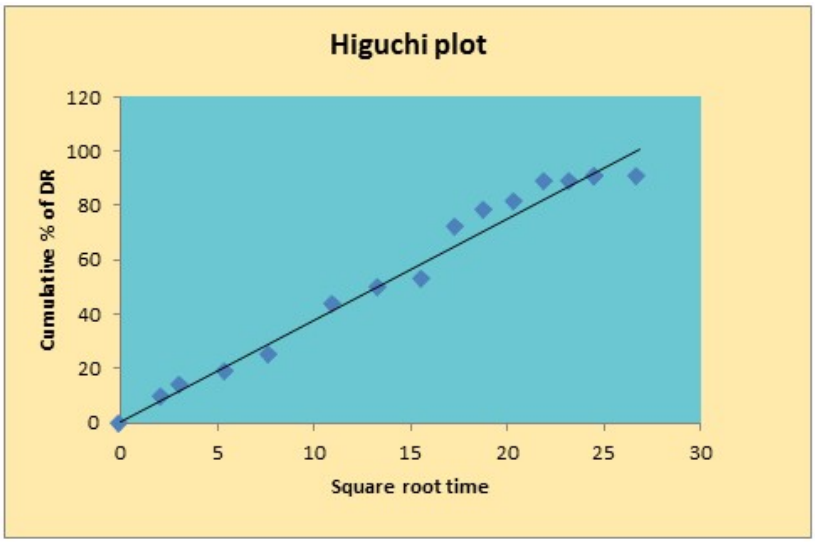

Figure 7: Higuchi plot of sofosbuvir tablet formulation

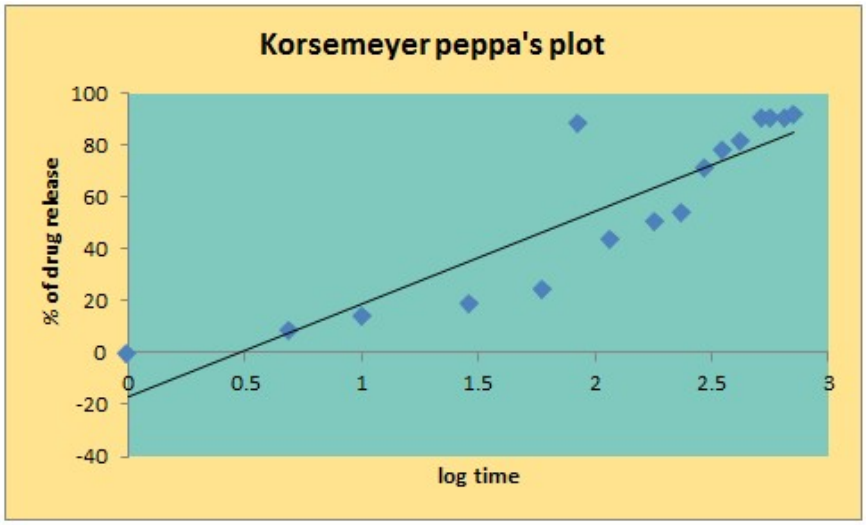

Figure 8: Korsemeyerpeppa's plot of SFBVR tablet formulation

Various pharmacokinetic effects, including zero order, first order, Higuchi model, and Korsemeyer, are fitted to the drug release data of controlled release tablets. Table 5 depicts the R^2 values of various pharmacokinetic models.

Table 5: *In-vitro* kinetic analysis (R^2 values)

	Zero order	First order	Higuchi	Korsemeyer peppa's
R^2 values	0.991	0.845	0.993	0.8087

The data of the *in vitro* release of drug encapsulated in the microspheres was fitted to a number of kinetic models to determine the mechanism of drug release. The material obtained was released under control due to the zero-order of the kinetics which demonstrated good linearity (R^2=0.991). The Higuchi plot (R^2=0.993) has shown that there is linearity, and gives more evidence to the diffusion mechanism. The Higuchi model was the best model that fitted the release kinetics of the controlled release tablet dosage form and exhibited zero order drug release with an anomalous diffusion (non-Fickian diffusion) mechanism.

CONCLUSION

Emulsion solvent evaporation was used to create SFBVR-MSPs utilizing a biocompatible polymer matrix. This kind of emulsion comprises of an aqueous phase that is emulsified with the medication, which is encapsulated, and an organic phase made up of a volatile solvent that has dissolved polymer. HPMC is employed as a polymer to delay the release of the medicine, while EC releases the drug gradually. The aqueous phase contains tween 80 to prevent MSPs from flocculating and coalescing. Based on the evaluation parameters F3 was selected as best formulation, further used for fabrication of controlled release tablets. 10 µm size range containing MSPs were successfully formulated into controlled release tablet dosage forms with 95 % of drug release for 12 hours. The release kinetics of controlled release tablets fitted into Higuchi model and showed zero order drug release with Non Fickian diffusion. Post formulation parameters of tablets were comply with official specifications. Concluded that the polymer used to improve the flow property and sofosbuvir release was controlled over extended period of time from microspheres.

Conflict of Interest:

No conflict of interest

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