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Formulation, Development and Evaluation of Bi-Layer Tablet of Anti HIV Drug

Reena Malviya[1]*, Dharmendra Singh Rajput[1], Shailesh Jain[1]

[1]Patel College of Pharmacy, Ratibad, Bhopal (M.P) India

ABSTRACT

In the last decade, interest in developing a combination of two or more Active Pharmaceutical Ingredients (API) in a single dosage form (bi-layer tablet) has increased in the pharmaceutical industry, promoting patient convenience and compliance. The Bi-layer tablets have been developed to achieve controlled delivery of different drugs with pre-defined release profiles. Bi-layer tablets can be a primary option to avoid chemical incompatibilities between API by physical separation, and to enable the development of different drug release profiles (immediate release with extended release). Despite their advantages, due to the use of different materials and complex geometric boundaries between the adjacent layers, the mechanical structures of this drug delivery system have become quite intricate, requiring complicated tablet architectures as well as patient-friendly. Bi-layer tablets offer definite advantages over conventional release formulation of the same drug. Several pharmaceutical companies are currently developing bi-layer tablets. For a variety of reasons: patent extension, therapeutic, marketing to name a few. To reduce capital investment, quite often existing but modified tablet presses are used to develop and produce such tablets.

Keywords: Bi-layered tablet, API (Active Pharmaceutical Ingredients), adjacent layer, conventional release, insufficient hardness.

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***Address for Correspondence:**

Reena Malviya, Patel College of Pharmacy, Ratibad, Bhopal (M.P) India

INTRODUCTION

A tablet is mixture of active substance and excipients usually in powder form pressed or compacted into a solid. The excipients includes binders, glidents (flow-aids), and lubricants to ensure efficient tableting, disintigrants to ensure that the tablet breaks up in the digestive tract; sweeteners or flavours to mask the taste of the bad tasting active ingredients and pigments to make uncoated tablets visually attractive. A coating may be applied to hide the taste of tablets components, to make the tablet smoother and easier to swallow and to make it more resistant to environment extending its self life.

PREPARATION AND CHARACTERIZATION METHOD 17-19

1) Selection of Method for Compression:

The major challenge for tablet manufacture comes from the powder characteristics of material compressed. There are number of compression technology available in pharmaceutical industry. Tablets have been made by granulation, a process that imparts to be primary requisite to formulation for fluidity and compatibility on these bases granulation process can be divided as:

- Dry granulation method.
- Direct compression.
- Wet granulation.

Direct compression:

The term “direct compression” is defined as the process by which tablets are compressed directly from powder mixture of API and suitable excipients. No pretreatment of the powder blend by wet or dry granulation procedure is required.

2) Formulation Development:

Preparation of Instant Layer of Sofosbuvir (Phase-1)

Fast dissolving tablets of Sofosbuvir were prepared by direct compression method after incorporating different super disintegrants such as, crosscarmellose sodium (Ac-Di-Sol), crospovidone and sodium starch glycolate in different concentrations. The ingredients given below were weighed and mixed in geometric progression in a dry and clean mortar. Then the ingredients were passed through mesh #60.

Magnesium stearate as lubricant and talc as glidant were added in a final step and mixed, this blend was subjected to analysis of pre-compression parameters which included Angle of repose, Bulk density, Tap density, Carr's index and Hausner's ratio.

The Blend was compressed on 8 mm (diameter) fat punches on a 'Rimek mini press 16 station rotary compression machine. Eight formulations of Ranitidine hydrochloride granules were prepared and each formulation contained one of the three disintegrant in different concentration. Each tablets weighing 150mg, were obtained. Composition of tablets is mentioned in Table 1.

Table 1: Composition of Sofosbuvir Fast Dissolving Tablets

Ingredients(mg)	Formulation code								
	IF1	IF 2	IF 3	IF 4	IF 5	IF 6	IF 7	IF 8	IF 9
Sofosbuvir	100	100	100	100	100	100	100	100	100
Sodium Starch glycolate	10	15	20	-	-	-	-	-	-
Croscarmellose sodium	-	-	-	10	15	20	-	-	-
Crospovidone	-	-	-	-	-	-	10	15	20
Microcrystalline cellulose	29	24	19	29	24	19	29	24	19
Talc	5	5	5	5	5	5	5	5	5
Magnesium stearate	6	6	6	6	6	6	6	6	6
Total weight	150	150	150	150	150	150	150	150	150

Evaluation of Precompression Parameter [20-21]

1. **Bulk density:** Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. Accurately weighed amount of granules taken in a 50 ml capacity measuring cylinder was tapped for 100 times on a plane hard wooden surface and estimated the LBD and TBD, calculated by using following formulas.

$$\text{LBD (Loose Bulk Density)} = \frac{\text{Mass of Powder}}{\text{Volume of Packing}}$$

$$\text{TBD (Tapped Bulk Density)} = \frac{\text{Mass of Powder}}{\text{Tapped Volume of Packing}}$$

2. **Carr's Compressibility Index**: Percent compressibility of powder mix was determined by Carr's compressibility index, calculated by using following formula:-

$$\text{Carr's Index \%} = \frac{\text{TBD} - \text{LBD}}{\text{TBD}} \times 100$$

3. **Hausners ratio:** It is determined by comparing tapped density to the bulk density by using following equation:-

Housner's ratio = Tapped bulk density/loose Bulk density

Hausner's ratio value <1.25 shows better flow properties

Table 2: Results of pre-compressional parameters of Sofosbuvir

Formulation code	Parameters			
	Loose Bulk density(gm/ml)	Tapped bulk density(gm/ml)	Carr's Index (%)	Hausner's Ratio
IF1	0.42	0.52	19.231	1.238
IF2	0.45	0.55	18.182	1.222
IF3	0.48	0.54	11.111	1.125
IF4	0.46	0.52	11.538	1.130
IF5	0.45	0.58	22.414	1.289
IF6	0.43	0.56	23.214	1.302
IF7	0.42	0.54	22.222	1.286
IF8	0.43	0.53	18.868	1.233
IF9	0.45	0.49	8.163	1.089

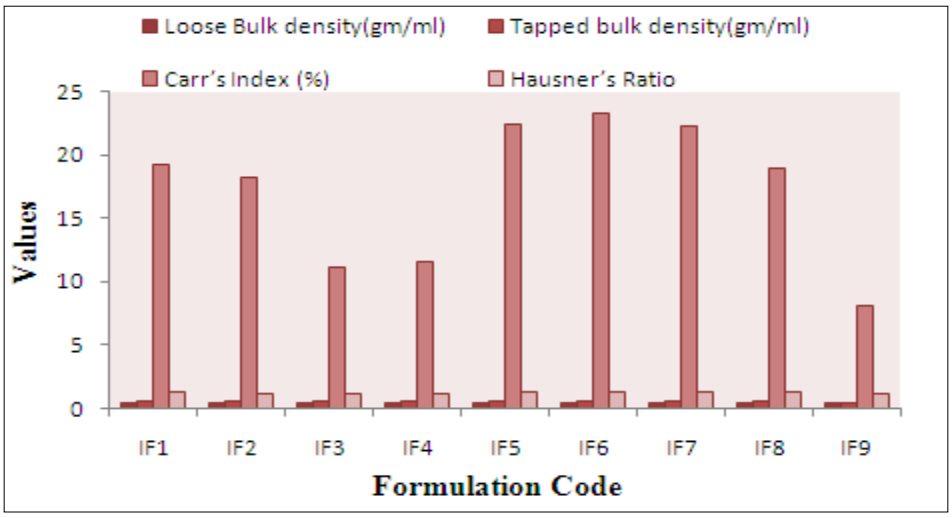

Figure 4: Graphical representation of Results of pre-compressional parameters of Sofosbuvir

Evaluation of post compression Parameter

1. Shape and colour of tablets:

Uncoated tablets were examined under a lens for the shape of the tablet and colour was observed by keeping the tablets in light[22]

2. Thickness test

Three tablets were picked from each formulation randomly and thickness was measured individually. It is expressed in mm and standard deviation was also calculated. The tablet thickness was measured using dial-caliper (Mitutoyo, Japan).

3. Weight variation test

Twenty tablets were selected randomly from each formulation and average weight was determined. The tablets were weighed individually and compared with average weight. The U.S Pharmacopoeia allows a little variation in the weight of a tablet. The following percentage deviation in weight variation is allowed.

4. Hardness test

The hardness of tablet was measured by Pfizer hardness tester and results were expressed in Kg/cm^2.

5. Friability test

For this, 20 tablets were taken from each formulation and the friability was determined using Roche friabilator. The equipment was run for 4 min at 25 revolutions per minute. The tablets were taken out, dedusted and reweighted and % friability was calculated. The friability was determined as the mass loss in percent according to Equation:-

$$\%\text{Friability} = (\text{Loss in weight}/\text{Initial weight}) \times 100$$

The test complies if tablets not lose more than 1% of their weight

6. Uniformity of drug content:

The test is mandatory for tablets with 10 mg or less weight of active ingredient. Ten randomly selected tablets from each formulation (F1 to F9) were finely powdered and Drug equivalent to 10 mg of drug dissolved in 10 ml 0.1 N HCL (simulated gastric fluid of pH 1.2 without enzymes) sonicated it for 20 minutes, till the entire drug leached out from complex, then the solution was filtered through what man filter paper No. 41. From this Solution take 1 ml and Diluted up to 100 ml with 0.1N HCL and the drug content was determined spectrophotometrically at 264.0 nm for Sofosbuvir.

Table 3: Results of Post-Compression parameters of all formulations

F. Code	Hardness test (kg/cm^2)	Friability (%)	Weight Variation (%)	Thickness (mm)	Drug content (%)
IF1	3.5	0.856	152	2.35	96.65
IF2	3.6	0.845	153	2.36	98.89
IF3	3.4	0.898	150	2.45	98.52
IF4	3.9	0.856	154	2.32	97.65
IF5	3.7	0.874	148	2.25	98.98
IF6	3.5	0.856	149	2.41	98.12
IF7	3.4	0.856	152	2.32	97.85
IF8	3.5	0.789	152	2.43	98.78
IF9	3.4	0.795	153	2.43	98.85

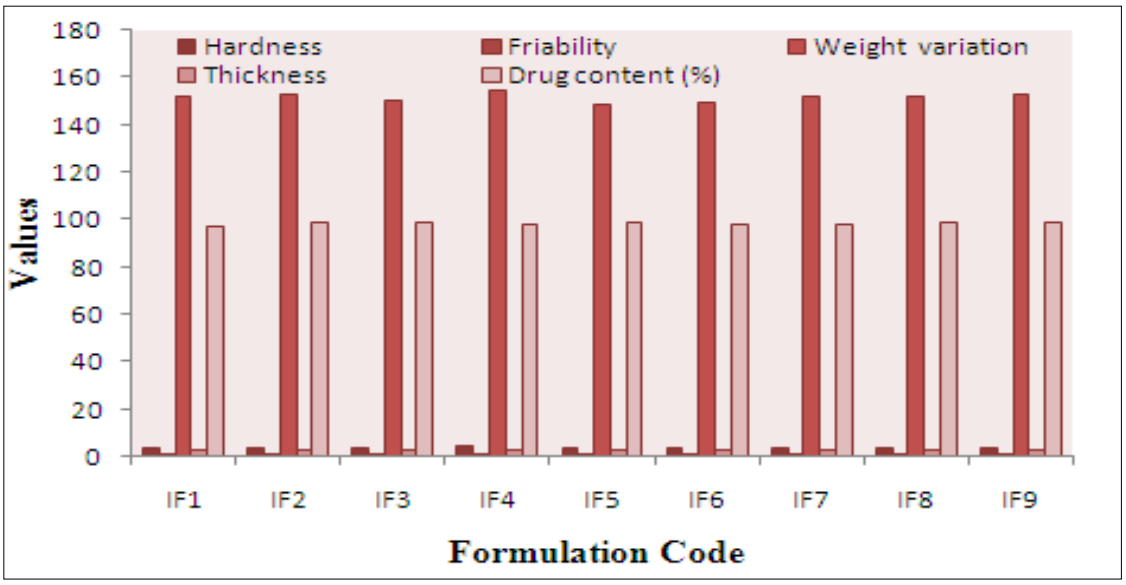

Figure 5: Graphical Representation of Post-Compression parameters of all formulations

Method for Preparation of Sofosbuvir Floating Gastro-retentive tablet [23]

Direct compression- was followed to manufacture the gas generating floating tablets of Sofosbuvir .Nine different formulations (F1, F2, F3, F4, F5, F6, F7, F8, & F9) were prepared by direct compression. All the polymers selected, drug and excipients were passed through sieve no. 40 before using into formulation. The amount and ratio of drug and polymers were weighed as per given in table No.4 and all the formulation were used for further evaluations parameters.

Polymers selected for tablets are-

- HPMC K 15,
- HPMC K4,
- PVP K30

Optimization of Gastro retentive floating tablets of Sofosbuvir floating tablets

Table 4: Various formulations of Sofosbuvir gastro retentive tablets

Excipients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Sofosbuvir	300	300	300	300	300	300	300	300	300
HPMC K 15	_	_	_	80	100	120	40	50	60
HPMC K 4	80	100	120	_	_	_	40	50	60
PVP K30	15	15	15	15	15	15	15	15	15
Citric acid	5	5	5	5	5	5	5	5	5
$NaHCO_3$	20	20	20	20	20	20	20	20	20
$Mg(C_{18}H_{35}O_2)_2$	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5
Lactose	70	50	30	70	50	30	70	50	30
Total Weight	500	500	500	500	500	500	500	500	500

Excipients like Sodium bicarbonate, citric acid anhydrous, Magnesium Stearate were selected for the study. Sodium bicarbonate and citric acid were used as gas generating agent. Citric acid was also used as an antioxidant. Steps involved in the manufacture of tablets, first the drug, polymer and other excipients selected were passed through 40-mesh sieve. Required quantity of drug, polymer and excipients were weighed properly and transferred into polyethylene bag and the blend was mixed for at least 15 min. The blend obtained was then lubricated by adding 1% magnesium stearate and again mixed for another 5 min.

Evaluation of tablets:-

All the tablets were evaluated for following different parameters which includes;

1. General Appearance

Five tablets from different batches were randomly selected and organoleptic properties suchas color, odor, taste, shape,

were evaluated. Appearance was judged visually.Very good (+++), good (++), fair (+) poor (-), very poor (- -).

2. Thickness and diameter

Thickness and diameter of tablets were determined using Vernier caliper. Five tablets fromeach batch were used, and an average value was calculated.

3. Drug content

Twenty tablets were taken and amount of drug present in each tablet was determined. The tablets were crushed in a mortar and the powder equivalent to 100 mg of drug was transferred to 100 ml standard flask. The powder was dissolved in 50 ml of 0.1 N HCL and made up to volume with of 0.1 N HCL. The sample was mixed thoroughly and filtered through a 0.45µ membrane filter. The filtered solution was diluted suitably and reacts with dye and analyzed for drug content by UV spectrophotometer at a λ_{max} of 264.0 nm using of 0.1 N HCL as blank.

4. Hardness

For each formulation, the hardness of five tablets was determined using the Monsanto hardness tester (Cadmach)

5. Friability

The friability of a sample of 10 tablets was measured using a Friability tester (Electro Lab).Ten tablets were weighed, rotated at 25 rpm for 4 minutes. Tablets were reweighed afterremoval of fines (dedusted) and the percentage of weight loss was calculated.

6. Uniformity of weight

Twenty tablets were randomly selected from each batch individually weighed, the average weight and standard deviation of 20 tablets was calculated.

7. In vitro buoyancy studies:

In vitro buoyancy was determined by floating lag time as per the method described below. The tablets were placed separately ina100 ml glass beaker containing simulated gastric fluid (SGF), pH1.2 as per USP. The time required for the tablet to rise to the surface and float was determined as floating lag time.

8. Dissolution rate studies

In vitro drug release of the sample was carried out using USP- type II dissolution apparatus (Paddle type). The dissolution medium, 900 ml 0.1N HCL was placed into the dissolution flask maintaining the temperature of 37±0.50ºc and rpm of 75.One Sofosbuvir tablet was placed in each basket of dissolution apparatus. The apparatus was allowed to run for 10 hours. Sample measuring 5 ml were withdrawn after every 1 hour up to 10 hours using 10 ml pipette. The fresh dissolution medium (37⁰C) was replaced every time with the same quantity of the sample. From this take 0.5 ml and dilute up to 10 ml with 0.1 N HCL and take the absorbance at 264 nm using spectroscopy.

Table 5: Results of Post Compression Properties of Sofosbuvir FGR Tablets

Formulation code	Thickness (mm)	Hardness (kg/cm2)	Weight variation (mg)	Friability (%)	Drug content (%)
F1	3.95	5.2	505	0.895	98.85
F2	3.85	5.3	510	0.852	98.99
F3	3.68	5.4	508	0.789	98.65
F4	3.78	5.2	505	0.856	97.89
F5	3.85	5.4	506	0.745	98.45
F6	3.78	5.2	504	0.658	99.56
F7	3.82	5.3	498	0.980	98.89
F8	3.68	5.1	495	0.965	98.78
F9	3.45	5.2	508	0.745	99.12

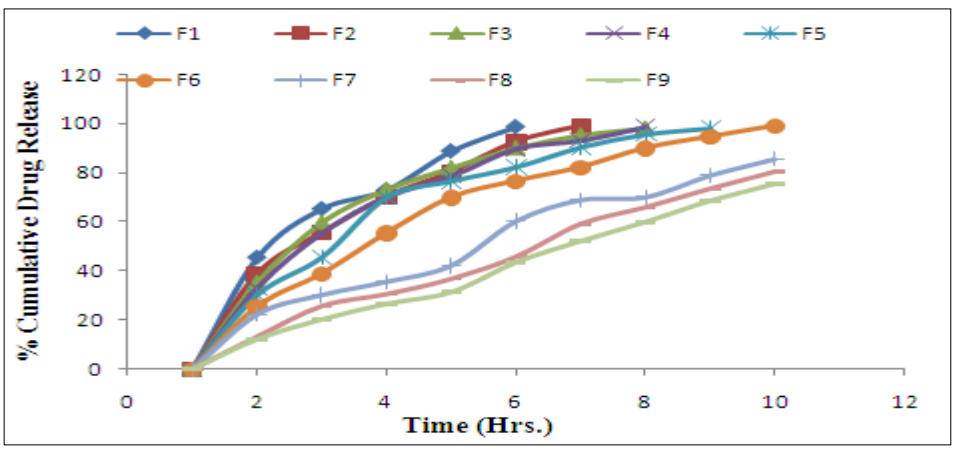

Figure 6: Graph of In-vitro Drug Release Study of GRF Tablets

In vitro drug release study of Gastro retentive floating tablet:

Tablet 6: In-vitro Drug Release Study of GRF Tablets

Time	% Cumulative Drug Release								
(hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0.5	39.78	36.65	33.45	30.12	25.65	**22.35**	18.56	15.23	11.56
1	45.65	43.23	40.45	38.78	35.65	**36.65**	30.25	25.65	20.32
1.5	59.98	55.45	52.56	50.12	49.98	**45.58**	35.65	30.45	26.65
2	75.56	69.98	65.65	63.32	62.12	**56.65**	42.25	36.65	31.47
3	82.45	80.45	78.89	75.65	73.65	**65.89**	53.65	45.65	43.65
4	95.65	92.25	90.25	88.98	84.65	**73.45**	68.98	58.98	55.45
6		98.78	96.65	93.65	90.12	**88.98**	70.12	65.78	60.12
8			98.89	98.89	97.45	**95.65**	78.98	73.32	68.78
12						**99.12**	89.98	81.45	79.98

Formulation development of bi-layer tablet[25]

Optimized formulation IF-7 of Instant release layer and optimized formulation of F-6 for control release used for formulation of Bi-layer tablet.

Evaluation of bi-layer tablets-

All the tablets were evaluated for following different parameters which includes;

1. General Appearance[24]

Five tablets from different batches were randomly selected and organoleptic properties such as color, odor, taste, shape, were evaluated. Appearance was judged visually.

Very good (+++), good (++), fair (+) poor (-), very poor (- -).

2. Thickness and diameter

Thickness and diameter of tablets were determined using Vernier caliper. Five tablets fromeach batch were used, and an average value was calculated.

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5. Uniformity of weight

Twenty tablets were randomly selected from each batch individually weighed, the average weight and standard deviation of 20 tablets was calculated.

6. Drug content

Twenty tablets were taken and amount of drug present in each tablet was determined. The tablets were crushed in a mortar and the powder equivalent to 5 mg of Sofosbuvir was transferred to 10 ml standard flask. The powder was dissolved in 10 ml of 0.1 N HCL and made up to volume with 0.1 N HCL. The sample was mixed thoroughly and filtered through a 0.45µ membrane filter. The filtered solution was further diluted 0.2 ml to 10 ml suitably 10 ppm solutions and determines the Concentration of drug at 264 nm.

7. Dissolution rate studies-

In vitro drug release was performed according to the USP dissolution apparatus II at 50 rpm and 37±0.5ºC temperature over a 12 hrs period for Sofosbuvir bi-layer tablets using an automated paddle dissolution system (Labindia). A minimum of 6 tablets per batch were tested. The media used was 0.1N HCL at a pH 1.2 and a volume of 900 ml was maintained at 37±0.5 ◦ C. Test sample (1ml) was withdrawn at particular time interval and replaced with fresh dissolution media maintained at the same temperature and the concentration of dissolved drug was determined using U.V. (Labindia 3000 plus) spectrophotometer at λ_{max} 264 nm.

SUMMARY ANA CONCLUSION

Preliminary study showed that sofosbuvir is White to off white powder and odourless powder. It is freely soluble in methanol and ethanol, soluble in 0.1 N HCL, sparingly soluble in 0.1 N NaOH, The melting point was in the range of 198ºC which is compliance with the standard value. Identification of Sofosbuvir was performed by UV/VIS Spectroscopy. The 10 µg/ml solutions of Sofosbuvir was scanned in the range of 200-400nm to determine the λ_{max} for drug. The λ_{max} of sofosbuvir was found to be 264 nm. From the respective stock solution (1mg/ml) different concentration of 5, 10, 15, 20 and 25µg/ml Sofosbuvir was prepared and scanned in UV region. Their absorbances were noted at 264.0 nm and calibration curve was plotted as absorbance vs concentration and their linearity range was determined. From the FT-IR data of the physical mixture obviously function of drug have stayed unaltered including forces of the peak. This proposes and the procedure drug and excipient has not responded with the drug to offer ascent to reactant items. So there is no interaction between them which is in favour to proceed for formulation of vesicular drug delivery system. Preformulation studies reported that the formulation of floating of Sofosbuvir can be prepared with appropriate methods. A study involving preparation and evaluation of bi-layer tablets of Sofosbuvir were made. Physico-chemical parameters of bi-layer tablets were performed. In vitro drug release profiles of bi-layer tablets were performed. A dissolution study shows the release of Sofosbuvir. The Instant layer of sofosbuvir release approx 98.32% drug within 15 minutes and control floating

layer sofosbuvir shows release up to 12 Hours Approx 99.12 % of Drug release in 12 hour.

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