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Exploration of melt granulation technique for the development of entecavir monohydrate tablets using 3^2 factorial designs

Ramana Kumari Avirneni [1,*] and Prakash Nathaniel Kumar Sarella [2]

[1] *Department of Pharmaceutics, Netaji Institute of Pharmaceutical Sciences, Kazipet, Warangal, State of Telangana – 506003, India.*
[2] *Department of Pharmaceutics, Faculty of Pharmacy, Aditya College of Pharmacy, ADB Road, Surampalem, East Godavari, Andhra Pradesh-533 437, India.*

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Abstract

This research work aims to fabricate fast-release tablets of entecavir monohydrate using a novel melt granulation technique and optimize the proportion of xylitol and mannitol using a 3^2 factorial design. entecavir monohydrate, a medication used for treating hepatitis B virus (HBV) infection, was used as a model drug. The fast-release tablets were designed to avoid fluctuations in plasma drug concentration and increase the bioavailability of entecavir monohydrate. The FTIR spectra of pure entecavir monohydrate were compared against polymers which had no interaction. The pre-compression and post-compression parameters were found to be within the desired range. The results of the drug release studies indicate that the formulations were able to release the drug within the desired range of 60-80% within 10 minutes. The study concludes that the melt granulation technique can be used to develop fast-release tablets of entecavir monohydrate with good compressibility, flow characteristics, and mechanical strength.

Keywords: Entecavir monohydrate; Fast disintegrating tablets; Melt granulation; Factorial design; Optimization.

1. Introduction

Melt granulation is a process used to produce granules by adding either a molten binder or a solid binder that melts during fabrication of the tablet. This technique can be broken down into 3 stages: wetting-nucleation, coalescence, and attrition-breakage (1). In melt granulation, a binder makes up 10-30% of the total weight of the fine particles. The binder should be meltable and its melting point should be between 50-200°C. Hydrophilic molecules are often used as binders for immediate-release dosage forms, while hydrophobic molecules are used for prolonged-release dosage forms (2). One advantage of melt granulation is that it doesn't employ solvents, and thus streamline the process and eliminates the need for drying. This can also reduce processing time.

Entecavir monohydrate is used in the management of Hepatitis B virus (HBV) infection(3). The objective of this research is to fabricate tablets of entecavir monohydrate utilizing the melt granulation technique and fine-tune the proportion of xylitol and mannitol until the formulation has optimal characteristics using 3^2 factorial design. Additionally, melt granulation leads to a uniform dispersion of fine particles and offers good stability at different pH levels and levels of moisture(4). The study intends to show that melt granulation can be employed to generate a multifaceted, compressible excipient for usage in the pharmaceutical industry (5). In this research work, entecavir monohydrate was used as a drug candidate to develop fast-release tablets using xylitol and mannitol through a novel melt-granulation technique. The fast-release tablets aimed to avoid fluctuations in plasma drug concentration and increase the bioavailability of entecavir monohydrate.

*Corresponding author: Ramana Kumari Avirneni

2. Material and methods

Entecavir monohydrate is provided by Dr. Reddy's Ltd, Hyderabad, Telangana. mannitol, xylitol, and Sodium Hydroxide are obtained from S.D Fine chemicals Ltd, Mumbai. Talc is sourced from Reidel Chemicals, Hapur. Disodium hydrogen phosphate is obtained from Merck Pvt. Ltd. Mumbai. All the chemicals used are of analytical grade to prevent source variation during the experiment.

2.1. Drug-excipient incompatibility study

Fourier Transform Infrared (FTIR) spectroscopy was used to analyze the physical mixtures of entecavir monohydrate with the excipients xylitol, mannitol, and Talc (6) using FTIR spectrophotometer Shimadzu 1700. The drug and the excipients were mixed in a 1:1 ratio and the functional groups are assessed by scanning from 4000 cm^{-1} to 400 cm^{-1}

2.2. Construction of standard calibration curve

Accurately weighed 10 mg of entecavir monohydrate was first dissolved in 10 ml of methanol to result in a stock solution of 1000 µg/ ml. This stock solution is subsequently diluted with 0.1 N HCl to result in various concentrations of 5 to 30 µg/ml. The absorbance of the solutions of various concentrations was measured in a Ultra-violet (UV) –visible Double beam spectrophotometer (Model Elico SL 159) at 265 nm using 0.1N HCl as blank (7). The equations for the best-fit straight line were obtained to determine the slope and intercept which were later used for the estimation of entecavir monohydrate. The values of the coefficient of regression (r^2) are obtained to determine the linearity of the best-fit line.

2.3. Preparation of entecavir monohydrate tablets using melt granulation technique

The independent variables in the study were the amounts of mannitol (X1) and xylitol (X2) at 3 levels, 30%, 40% and 50%. The dependent variables were the disintegration time, wetting time, and % Cumulative drug release (CDR) at 10 minutes. A multiple linear regression analysis with a 95% confidence interval ($p<0.05$) was performed using Design Expert 7.1.5.0® (Stat Ease Inc., Trial Version) to determine the significant terms in the final polynomial equations. A 3^2 factorial design was used to investigate the combined effects of the independent variables on the best formulation and the necessary concentration for the desired drug release from the dosage form (8).

Table 1 Composition of different formulations as per 3^2 full factorial design

Formulation Code	Entecavir monohydrate(mg)	Independent variables		Talc (mg)
		Mannitol (%)*	Xylitol (%)*	
F1	1	50	50	4
F2	1	50	40	4
F3	1	50	30	4
F4	1	40	50	4
F5	1	40	40	4
F6	1	40	30	4
F7	1	30	50	4
F8	1	30	40	4
F9	1	30	30	4

*Coded as 50%= +1, 40% = 0, and 30% =-1 in 3^2 factorial design

Mannitol, which has a melting point of 166^0C, and xylitol, which has a melting point of 97^0C, were used as the higher and lower melting point sugar alcohols respectively. The drug entecavir was combined with sugar alcohols and heated to 100^0C, melting the lower melting point sugar alcohol. The mixture, with the composition specified in Table 1, was then passed through a mesh screen with openings of 0.177 inches, dried, and passed through another mesh screen with openings of 0.042 inches, retaining only the particulate that could not pass through openings of 0.0101 inches. The granules were coated with talc and compressed using a 0.315 inch punch on a single-station tablet press (Cadmach Machines Ltd) (2).

2.4. Pre-compression parameters

Evaluation of the powder blend was performed by determining the bulk density and tapped density, carr's compressibility index, angle of repose, and Hausner's Ratio (9).

2.4.1. Bulk and tapped density

A 5 gram sample of powder from each formula was added to a volumetric cylinder holding 25 milliliters. The initial volume of the powder in the cylinder was recorded. Then, the cylinder was dropped from a height of 0.1 meters (2.5 cm) onto a hard surface at 2 second intervals. The process of dropping the cylinder and recording the volume was repeated until no further change in volume was observed.

$$\text{Bulk density} = \frac{\text{Weight of the powder (gm)}}{\text{Initial volume (mL)}}$$

$$\text{Tapped density} = \frac{\text{Weight of the powder (gm)}}{\text{Final volume after tapping (mL)}}$$

2.4.2. Carr's Compressibility index

The compressibility index is a significant metric that can be determined from the bulk and tapped densities. In general, less compressible materials are more flowable. A material with a compressibility index of less than 12% is considered to be free-flowing (10).

$$\text{Compressibility index} = \frac{\text{Initial volume} - \text{Final volume}}{\text{Initial volume}} * 100$$

2.4.3. Angle of repose

The flow characteristics of a powder were assessed by calculating the angle of repose. This is the largest angle that can be formed between the surface of a freestanding powder pile and a horizontal plane. The angle of repose can be calculated using the formula:

$$\text{Angle of repose } \theta = \tan^{-1}\frac{\text{height of the pile (cm)}}{\text{radius of the pile (cm)}}$$

A precise weight of the sample was taken. A funnel was attached to a stand so that the tip of the funnel was 6 cm above the surface(9). The sample was poured through the funnel slowly to form a heap. The height and circumference of the powder heap were then measured.

2.4.4. Hausner's ratio

The Hausner ratio indicates a powder's flow ability and is calculated by dividing the tapped density by the bulk density. A Hausner ratio below 1.2 signifies a powder that flows freely(10).

2.5. Evaluation of tablets

2.5.1. Size and Shape

The size, shape, and other characteristics of tablets can be identified, tracked, and regulated. The shape and dimensions of compressed tablets are established by the dies used during compression. Tablet thickness is the only metric that can be linked to the process. To determine thickness, 10 tablets were selected and their thickness and diameter were measured using vernier calipers. The average thickness and diameter were then calculated (11).

2.5.2. Hardness

Tablet hardness also called tablet-crushing strength is defined as the force required to break a tablet in a diametric compression test. The test is performed using a Monsanto tablet hardness tester (Perfit instruments). The tablet is placed between two anvils, a force is applied, and the strength at which the tablet breaks is recorded. The test is performed on 3 tablets and the average value of hardness is recorded.

2.5.3. Friability

The Roche friability tester (Campbell instruments) was used to determine tablet friability. 20 tablets were selected, weighed, and placed in the friabilator. The tablets were subjected to abrasion and impact by rotating a plastic chamber at 25 revolutions per minute for 4 minutes while dropping the tablets 6 inches with each revolution.. After the test, the tablets were cleaned and reweighed (12).

$$\% \text{ Friability} = 100\ (1 - \frac{\text{The initial weight of the tablets}}{\text{The final weight of the tablets}})$$

2.5.4. Weight variation test

20 tablets were randomly selected from each batch and weighed individually using an analytical balance (ASX2, Endeavour Instruments, India). The average tablet weight was calculated and the percentage deviation from the mean weight was determined for each tablet(13). For tablets weighing 130 mg or less, the weights of no more than 2 tablets should differ from the average weight by more than 10%. None of the tablets should deviate from the average weight by more than twice that amount, or 20% (14).

$$\% \text{ Weight variation} = \frac{\text{Mean weight of the 20 tablets} - \text{Weight of single tablet}}{\text{Weight of single tablet}} * 100$$

2.5.5. Content uniformity

Content uniformity was assessed for all nine formulations. Three samples from each formulation were analyzed using spectrophotometry. The mean value and standard deviation were calculated for all formulations (14).

2.5.6. Disintegration test

Tablet disintegration time was determined using a USP Tablet Disintegration Test Apparatus with 900 ml of distilled water and no disk. The time in seconds for tablets to completely disintegrate until no fragments remained in the #10 mesh screen was recorded(15).

2.5.7. Wetting test

The wetting time and capillarity of the tablets were evaluated using a standard method which involved placing the tablets in a 6.5 cm diameter petri dish filled with 10 ml of water at room temperature and measuring the time it took for the tablets to fully saturate (16).

2.5.8. Dissolution test

In vitro dissolution testing is carried out using LABINDIA DS 800 dissolution tester. A single tablet was placed in each dissolution vessel containing simulated gastric medium. After the designated time interval, 10 ml samples of the dissolution medium (0.1 N HCl) were taken, filtered, and the drug concentration was determined by measuring the absorbance at 265 nm. The percent drug release from various formulations at different time points is presented in Table 4. The drug release was fitted into various models such as zero-order, and first-order, and the results are shown in Table 5.

2.5.9. Similarity and difference factor

To assess similarity between dissolution profiles of different formulations, a model-independent approach using the difference factor (f1) and similarity factor (f2) was employed. The difference factor (f1) is the percentage difference between two curves at each point and represents the relative error between them. It demonstrates the percentage difference in dissolution at each time point. The similarity factor (f2) is the logarithmic reciprocal square root transformation of the summed squared error. It indicates the similarity in percentage dissolution between the two curves.. Difference factor f1 and similarity factor f2 were calculated by using the following formulae:

$$f_1 = \left\{\frac{\sum_{t=1}^{n}|R_t - T_t|}{\sum_{t=1}^{n} R_t}\right\} * 100$$

$$f_2 = 50 \log\left\{\left(1 + \frac{1}{n}\sum_{i=1}^{n}(R_t - T_t)^2\right)^{-0.5} * 100\right\}$$

Where "n" represents the number of time points, "Rt" is the dissolution of the reference product at time "t", and "Tt" is the dissolution of the test product at time "t". The similarity factor (f2) has been adopted by the FDA, the European Agency for the Evaluation of Medicinal Products (EMEA), and the Centre for Drug Evaluation and Research (CDER) as a standard to compare similarity between two or more dissolution profiles. The similarity factor (f2) is included in CDER guides such as guidance on dissolution testing of immediate-release solid oral dosage forms. (17) and guidance on Waiver of In-Vivo Bioavailability and Bioequivalence Studies for Immediate Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System (18). To be deemed similar and bioequivalent, dissolution profiles must have: A difference factor (f1) between 0 and 15 and a similarity factor (f2) between 50 and 100 (19).

3. Results and discussion

3.1. Analytical estimation

The absorbance values were plotted against the concentrations of entecavir monohydrate to obtain a standard calibration curve as shown in Figure 1. The method was found to conform to Beer's law within a concentration range of 5-30 µg/ml as evident from the r^2 value of 0.999 that suggests linearity. This method is later used to estimate the amount of the drug during drug assay and *in vitro* drug dissolution studies.

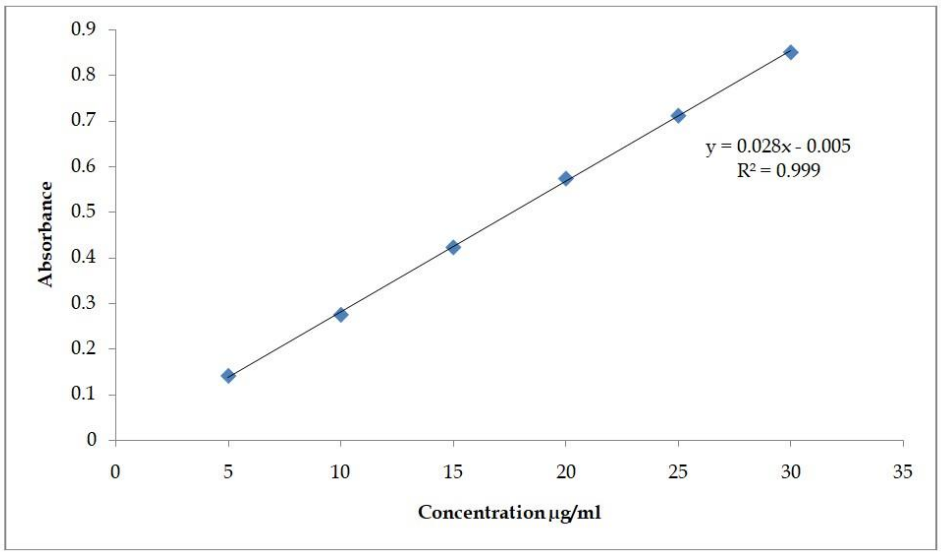

Figure 1 Standard calibration curve of entecavir monohydrate in 0.1N HCl

3.2. Drug drug-excipient incompatibility by Fourier Transform Infrared Spectroscopy (FTIR)

The FTIR spectra of pure entecavir monohydrate are compared against drugs mixed with polymers both before and after 30 days of storage. It is found that after storage, the FTIR spectrum of the drug mixture with excipients remained consistent with that of pure entecavir monohydrate, showing no interaction between the drug and excipients in the tablet. The FTIR spectra of all the drug-excipient mixtures have shown the characteristic peaks of the functional groups present in entecavir monohydrates such as C-O stretch (1631 to 1633 cm-1), C=O stretch (1705-1710 cm^{-1}), N-H stretch (3112 to 3170 cm^{-1}), and O-H stretch (3440 to 3446 cm^{-1}) are intact. This indicates no significant drug-excipient interaction between the drug and the excipients. This was confirmed by the absence of any new peaks or changes in the characteristic peaks in the FTIR spectrum as displayed in Figure 2.

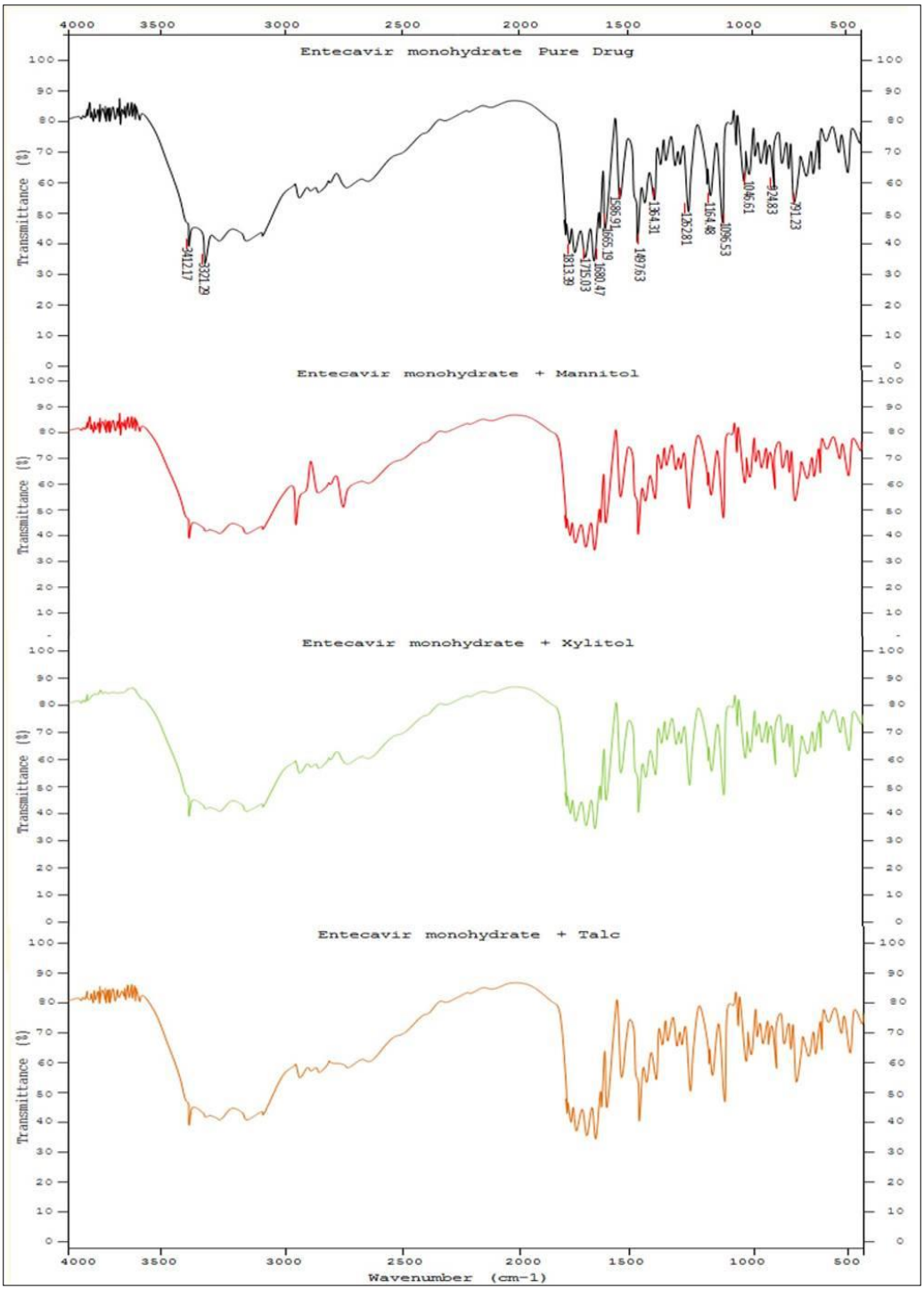

Figure 2 FTIR spectrum of pure drug and excipients

3.3. Evaluation of pre-compression parameters

The pre-compression parameters such as angle of repose, Carr's compressibility index, and Hausner's ratio indicated that it is free to moderate flow property of the powder blends, hence talc is added as a lubricant to the formulations to promote flowability (9)

3.4. Carr's Compressibility index

Carr's compressibility index was used to calculate the compressibility of the powder mixture. The results for all 9 formulations were between 4.26-15.27% (Table 2), indicating good compressibility (9).

3.5. Angle of repose

The values for the angle of repose for all the prepared formulations ranged from $26.6^0$to 27.8^0 (Table 2), which shows that they have fair to good flow characteristics.

3.6. Hausner's ratio

The values for Hausner's ratio of all the formulations were found to be between 1.04 and 1.18 (Table 2), indicating that the powder blends were free-flowing. To promotethefree flow of the powder blends and obtain dose uniformity glidants and lubricants are added to the powder blends before compression.

Table 2 Results of the pre-compression parameters

Formulation Batch Code	Angle of Repose (^{0})	Bulk Density (gm/ml)*	Tapped Density (gm/ml)*	Carr's Index	Hausner's Ratio
F1	27.5	0.376 + 0.11	0.427 + 0.24	11.94	1.13563
F2	26.8	0.404 + 0.39	0.434 + 0.17	6.91	1.07425
F3	26.5	0.436 + 0.47	0.456+ 0.32	4.38	1.0458
F4	27.8	0.424 + 0.54	0.43+ 0.19	1.39	1.01415
F5	27.6	0.426 + 0.38	0.445+ 0.15	4.26	1.04460
F6	26.9	0.238+ 0.89	0.275+ 0.34	13.45	1.15546
F7	26.6	0.236+ 0.71	0.276+ 0.28	14.49	1.16949
F8	27.4	0.233+ 0.76	0.275+ 0.19	15.27	1.18025
F9	27.8	0.231+ 0.76	0.272+ 0.28	15.07	1.17748

* mean ± standard deviation (S.D) n=3;

3.7. Post-compression parameters

The results of the post-compression parameters revealed that all the quality control parameters of the finished tablets such as thickness, hardness, friability, and disintegration test are within the limits. It can be concluded that melt granulation technique can be effective in preparing tablets with satisfactory quality control parameters (20).

3.8. Tablet thickness

The thickness of tablets from each formulation was determined by using a vernier caliper by selecting three tablets at random. The values were found to be uniform and were in the range of 3.84mm to 3.99mm (Table 3)

3.9. Hardness test

The hardness of the tablets was measured using a Monsanto tablet hardness tester. The results showed that the hardness was maintained within a range of 4.12 kg/cm^2 to 4.83 kg/cm^2 (Table 3). The hardness of all the formulations was consistent and had sufficient mechanical strength and hardness. The lower values of tablet hardness could be attributed to the melt granulation technique involved and suits the intended immediate release property of the tablets(1).

3.10. Friability test

The results of the friability test are presented in Table 3 and showed that the friability of the tablets was well within the acceptable range (<1%) for all formulations (14). Formulations F1 to F9 were found to have good mechanical strength. A representative image of the prepared formulations is shown in Figure 3.

Figure 3 Representative image of the prepared tablets of entecavir monohydrate

3.11. Disintegration test and wetting time

The disintegration time for the prepared formulations is in the range of 16.11 to 25.29 secs. It can be concluded that as the it can be observed that as the concentration of mannitol decreases and xylitol increases, the tablets are found to be more porous due to the loose inter-particular bonds formed during melt-granulation and lower melting point of xylitol helped in faster solvation with water molecules (21,22).

Table 3 Results of the post-compression parameters

S.No.	Formulation Code	Thickness* (mm)	Hardness* (kg/ cm²)	Friability(%w/w)	Disintegration Time*(secs)	Wetting Time*(secs)
1	F1	3.89 ± 0.02	4.15 ± 0.34	0.52	25.29 ± 2.32	23.11 ± 2.65
2	F2	3.99 ± 0.11	4.12 ± 0.21	0.43	19.23 ± 5.49	16.24 ± 4.71
3	F3	3.87 ± 0.07	4.11 ± 0.19	0.48	21.67 ± 3.46	18.97 ± 3.54
4	F4	3.95 ± 0.03	4.74 ± 0.22	0.39	17.75 ± 3.12	14.18 ± 2.38
5	F5	3.95 ± 0.04	4.21 ± 0.41	0.41	20.13 ± 1.94	16.37 ± 5.29
6	F6	3.96 ± 0.12	4.10 ± 0.27	0.53	18.19 ± 2.64	14.45 ± 2.31
7	F7	3.88 ± 0.09	4.83 ± 0.31	0.36	16.11 ± 3.02	11.63 ± 1.45
8	F8	3.84 ± 0.01	4.13 ± 0.56	0.49	22.15 ± 4.29	17.71 ± 2.57
9	F9	3.87 ± 0.02	4.09 ± 0.19	0.44	24.39 ± 3.47	19.82 ± 4.61

* mean±S.D., n=3

3.12. *In vitro* drug release studies

The results of the drug release studies are given in Table 4. Formulation F7 showed a better drug release of 98.45% in just 20 mins. The drug release order from the formulations is as follows (fastest release to slowest release basing on cumulative drug release at 10 mins):

F7>F8>F9>F4>F5>F6>F1>F2>F3

Formulations F7, F8, F9 that contain more concentration of mannitol and low concentration of xylitol that makes the tablets more porous due to the lower melting point of mannitol. This could have led to higher dissolution rates. As the concentration of xylitol increases such as with formulations F1, F2 and F3 the wetting time of the tablet increases resulting in lower dissolution rates. The FDA guidelines state that for two dissolution profiles to be considered similar and bioequivalent, the dissimilarity factor (f1) should be between 0 and 15, while the similarity factor (f2) should be between 50 and 100 (23). The release profiles from the developed drugs were compared with that of the marketed product Entehep (Zydus Cadila) and it was found that formulations F4, F5, F7, and F8 were not similar to the marketed drug but were better than it, as shown by the similarity and dissimilarity factors (results displayed in Table 5). The drug release from the prepared formulations is found to be superior when compared to the marketed formulation as evident from the similarity and difference factor.

Table 4 Comparative *in vitro* drug dissolution profiles of the prepared tablets with marketed formulation

Time (mins)	% Cumulative drug release									Entehep® Reference
	F1	F2	F3	F4	F5	F6	F7	F8	F9	
0	0	0	0	0	0	0	0	0	0	0
5	30.23	35.10	28.91	39.67	35.28	31.88	49.61	41.51	42.61	25.67
10	48.21	46.64	37.67	53.21	53.1	48.43	94.45	63.46	55.31	43.54
15	61.33	58.34	44.25	71.41	76.94	64.61	97.71	78.98	64.99	59.87
20	72.83	71.17	56.61	84.23	87.31	76.15	98.45	86.61	73.69	70.12
30	85.93	84.61	67.87	99.84	97.68	90.91	---	99.86	86.45	84.67
45	99.53	99.17	85.26	---	---	94.16	---	---	97.33	98.95
60	---	---	98.57	---	---	97.57	---	---	---	--

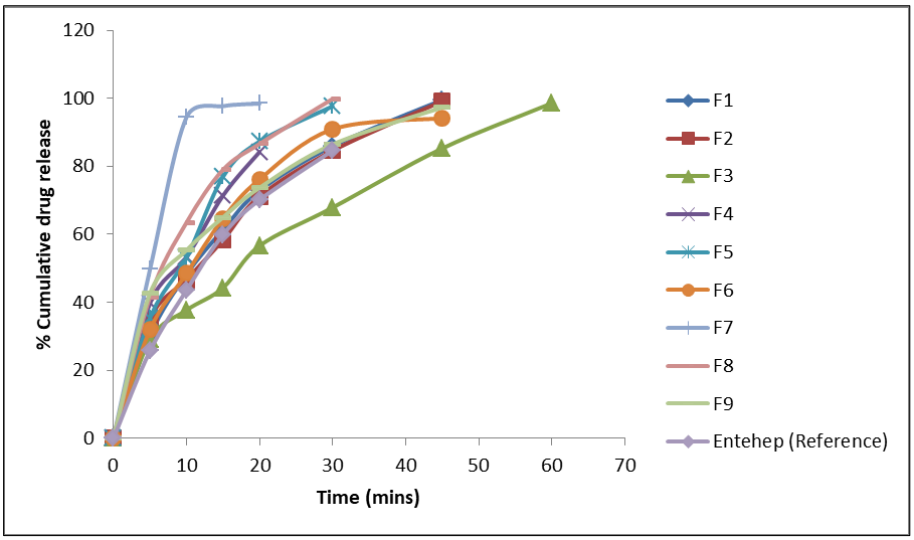

Figure 4 *In vitro* drug dissolution profiles of prepared formulations F1 to F9 in comparison with Entehep (Reference)

Table 5 Comparison of the similarity and dissimilarity factor between formulations and marketed product

Formulation	Similarity Factor	Dissimilarity Factor
F1	3.980	77.817
F2	3.189	70.909
F3	16.260	46.786
F4	9.001	18.777
F5	8.492	18.687
F6	6.091	66.004
F7	11.127	8.737
F8	3.239	18.120
F9	9.811	54.319

3.13. Curve fitting analysis

To determine the mechanism of drug release, the *in vitro* drug dissolution data was analyzed using both zero and first-order equations. The results showed that the drug release followed first-order kinetics as indicated by the higher regression coefficient (r^2) values for the first-order release model (0.892 to 0.977) compared to the zero-order release model (0.748 to 0.972) as shown in Table 6.

Table 6 Drug release kinetics

Formulation	Zero Order Plot		First Order Plot		Best Fit Model
	K	r^2	K	r^2	
F1	2.050	0.871	0.110	0.895	First Order
F2	2.001	0.878	0.096	0.906	First Order
F3	1.472	0.892	0.062	0.921	First Order
F4	3.148	0.814	0.195	0.911	First Order
F5	3.201	0.972	0.124	0.892	First Order
F6	1.436	0.748	0.062	0.981	First Order
F7	4.9	0.803	0.227	0.938	First Order
F8	3.113	0.842	0.200	0.857	First Order
F9	1.858	0.799	0.073	0.977	First Order

K= rate order constant, r^2 = coefficient of regression

3.14. Multiple linear regression models for disintegration time, wetting time, and % Cumulative drug release

The multiple linear regression equations for disintegration time, wetting time and % CDR at 10 mins as per the prediction model generated are as follows:

$$\text{Disintegration Time} = 20.22 + (0.050 * \text{mannitol \%}) - (0.083 * \text{xylitol \%}) + 3\ \text{mannitol\%} * \text{xylitol \%}$$

$$\text{Wetting Time} = 16.44 + (0.167 * \text{mannitol \%}) - (0.500 * \text{xylitol \%}) + 3\ \text{mannitol\%} * \text{xylitol \%}$$

$$\%\text{CDR} = 55.61 - (13.45 * \text{mannitol \%}) + (9.08 * \text{xylitol \%})$$

It can be observed from the above equations, that the positive signs associated with mannitol concentration indicates a direct relationship with the dependent variables (disintegration time, wetting time, and %CDR) while negative signs

associated with the xylitol concentration is detrimental to the dependent variables and the model parameters are shown in Table 7. The same is proved by looking at the contour plots for each variable in the Figures 5, 6 and 7.

Table 7 Multiple linear regression model for the dependent variables

Response	R^2	Adjusted R^2	Standard deviation	Probability > F
Disintegration time (min)	0.957	0.945	3.14	0.024
Wetting time (min)	0.945	0.929	2.60	<0.0001
% CDR at 10 min	0.955	0.909	9.23	0.0146

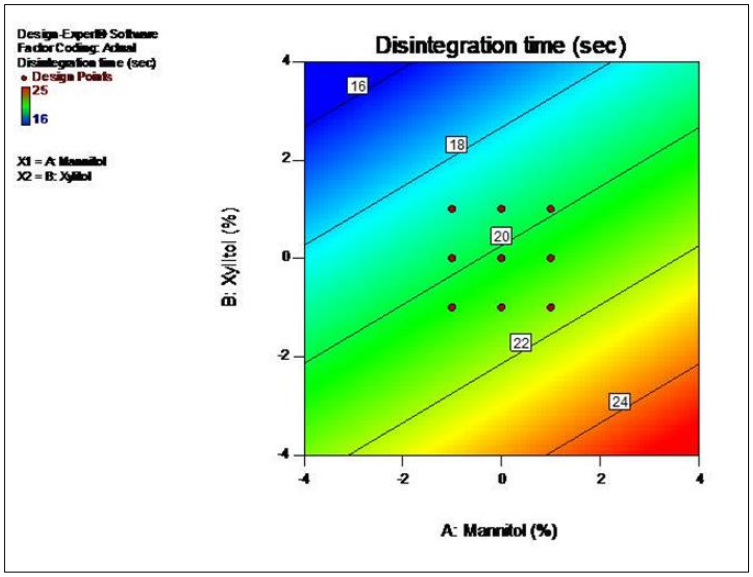

Figure 5 Contour plot of the dependent variable- disintegration time

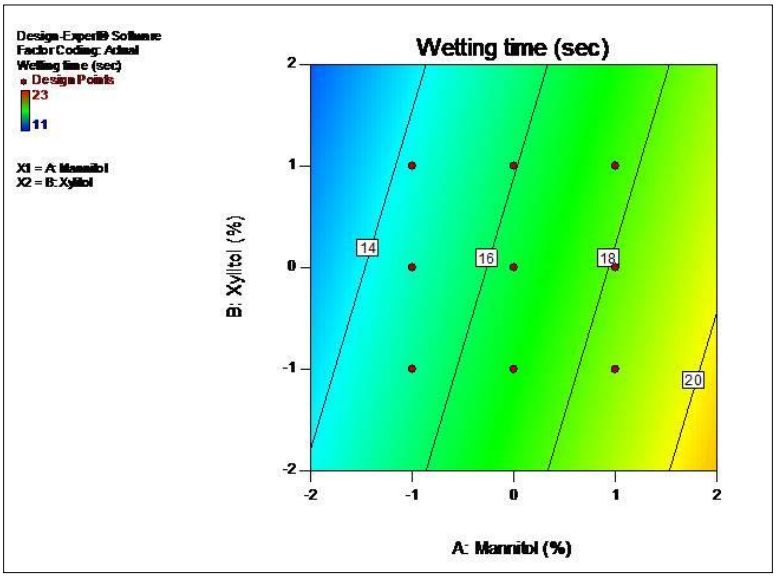

Figure 6 Contour plot of the dependent variable- disintegration time

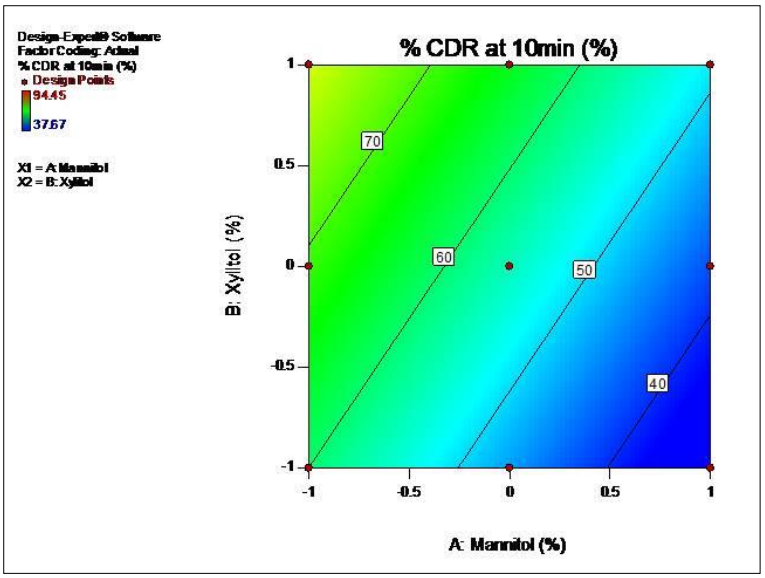

Figure 7 Contour plot of the dependent variable- disintegration time

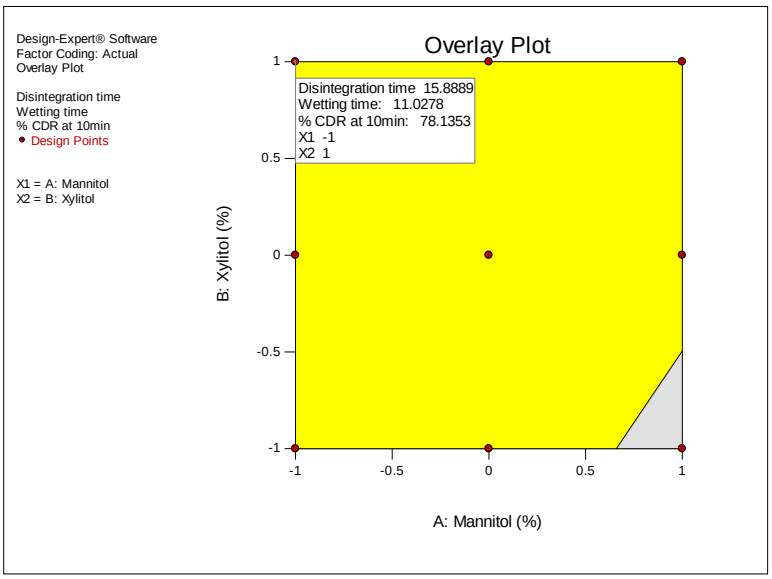

Figure 8 Overlay plot of the optimization parameters for the optimized model

Table 8 Comparison of the responses from the model with the actual experimental values

Description	Disintegration time (min)	Wetting time (min)	% CDR at 10 min
Model predicted	15.88	11.02	78.13
Experimental value (F7 formulation)	16.11	11.63	94.45
% Difference	1.5%	5.3%	17%

The modeling aimed to find the formulation with the fastest disintegration and drug release, as well as the shortest wetting time. According to the model, formulation F7, with a low amount of mannitol and a high amount of xylitol, would achieve the optimal response values (shown in figure 8). Experimental tests of F7 verified the model's predictions, with the actual results reasonably close to the modeled optimal values. This indicates that the model is reasonably accurate in predicting how changes to the formulation will impact the key outcomes. The model is good at predicting the

responses of disintegration time (difference of 1.5%) and wetting time (difference of 5.3%) while it is poor at predicting % cumulative drug release (difference of 17%) which could be attributed to the initial burst release of the drug from the formulation upon exposure to simulated gastric model. The results of the comparison are shown in the table 8

4. Conclusion

The study aimed to develop fast-release tablets of entecavir monohydrate using the melt granulation technique with xylitol and mannitol as excipients. These tablets were developed to improve patient compliance and achieve prompt release of the drug in the treatment of hepatitis B virus (HBV) infection. The tablets were evaluated for flow properties, thickness, hardness, and friability, and the results showed that they were mechanically stable, had good flow properties, and prompt drug release. Tablets containing 50% xylitol and 40% mannitol were found to demonstrate:Lesser disintegration time, Sufficient hardness, Prompt drug release. There is formation of interparticle bonds due to melting of xylitol and solidification upon cooling, imparting hardness and integrity to the tablets.The water-soluble nature of the sugars aids faster disintegration of the tablet.

Compliance with ethical standards

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Disclosure of conflict of interest

The Authors declare that there is no conflict of interest.

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Author's short biography

	**Ramana Kumari Avirneni,** Over the past 20 years, in the process of knowledge acquisition on both APIs and the finished solid oral dosage forms, I have been grown as a dynamic Regulatory dossier submission specialist executing successful dossier filing and approvals to major regulated markets like EU, UA, Australia, Canada and also to Russia, Brazil, LATAM, MENA and Row regions. Continuous striving for the passion is the reason behind my current position.
	**Prakash Nathaniel Kumar Sarella,** Pharmaceutical scientist with a passion for innovative drug delivery solutions. Over 6 years of experience in drug delivery research and development. Expertise in nanomedicine, liposomes, polymer therapeutics, antibody-drug conjugates, and microneedle technologies.