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FORMULATION AND EVALUATION OF IMMEDIATE RELEASE TABLET OF ENTECAVIR FOR HEPATITIS-B

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Abstract: Abstract In present investigation an attempt has been made to formulation and evaluation of immediate release dosage form of entecavir drug. Optimization studies were done for the selection of glidant, lubricant and coating materials. Evaluation of granules was done on the basis of preformulation studies. Pre compression and post compression parameters were evaluated for optimization. The prepared tablets were evaluated for physicochemical properties. The in- vitro release studies were performed as per USP and compared with marketed product. The release of Entecavir were analysed by high performance liquid chromatography (HPLC). Comparative dissolution studies and assays between optimized formulation and reference product showed better release and equivalent drug content. Stabilities studies were performed in both blister as well as cold form blister packings. Stabilities studies revealed the suitability of blister package in comparison to the cold form blister packing. The drug used in this formulation is used for the treatment of Hepatitis-B. Lactose monohydrate is used as diluent in tablet formulation which is safe to diabetic patients.

Keywords: Entecavir, Hepatitis-B, Immediate Release, Blister packing, Lactose monohydrate.

Introduction:

Tablet may be defined as the solid pharmaceutical dosage forms containing drug substances with or without suitable diluents and prepared either by compression or moulding method. They have been in wide spread use since the latter part of the 19th century and their popularity continues. The term compressed tablet is believed to have been first used by “JOHN WYETH”. Tablets remain popular as a dosage form because of the advantages afforded both to the manufacturer and the patient.

TYPES OF TABLETS

Tablets are classified as follows:

1. According to the drug release rate from the tablet.
2. According to the method of manufacturing.

According to the route of administration or function.

IMMEDIATE RELEASE DRUG DELIVERY SYSTEM[6]

Definition

Immediate release drug delivery system is also conventional type of drug delivery system as it is defined as – Immediate release tablets are designed to disintegrate and release their medicaments with no special rate controlling features such as special coatings and other techniques.

1.1MECHANISM OF ACTION OF ENTECAVIR

Entecavir is a guanosine analogue with activity against hepatitis B virus. Natural deoxyguanosine binds with the polymerase and thus helps in the transcription and replication of the viral DNA. Entecavir which is a nucleoside analogue competes with the natural deoyguanosine. Hence it is called nucleoside reverse transcriptase inhibitor upon entry in to the cell, this requires subsequent phosphorylation by intracellular enzymes to generate Entecavir -triphosphate which binds with the polymerase enzyme and thus display activity against three synthetic activities of the HBV polymerase.

1. The protein linked priming activity in the generation of m-RNA of virus.
2. RNA-directed 1st strand DNA synthesis or reverse transcription (RT).
3. DNA replication.

In addition Entecavir displays higher intrinsic potency than other NRTI's in the cell culture, enzymatic ally invitro and in clinical trials. The low therapeutic dosage of the Entecavir is primarily due to the intrinsic property of Entecavir triphosphate against HBV-RT as well as the efficiency of intracellular conversion to Entecavir-triphosphate. The Entecavir triphosphate has an intracellular half-life of 15 hours.

The othernucleotide analogues (NAs) act by direct inhibition, through competitive binding with endogenous substrates or through incorporation into the viral DNA to act as chain terminators. Entecavir drug has a high barrier to resistance when compared to other drugs,as this requires additional three mutations to the mutations which are responsible to develop resistance against other drugs like Lamivudine.

2.Materials and methods :

Manufacture of the tablet blend:

In the tablet pressing process, the main guideline is to ensure that the appropriate amount of active ingredient is in each tablet. Hence, all the ingredients should be well mixed. If a sufficiently homogenized mixture of the components cannot be obtained with simple blending processes, the ingredients must be granulated prior to compression to assure an even distribution of the active compound in the final tablet.Powders that can be mixed well do not require granulation and can be compressed into tablets through direct compression.

Direct compression:

This method is used when the ingredients can be blended and placed in a tablet press to make a tablet without any of the ingredients having to be pre-processed.

This requires the active ingredient to have appropriate physical and chemical properties, such as good compactibility and low stickiness. Direct compression is often preferred because of its simplicity and relatively low cost, but may not always be technically feasible.

Granulation is the process of combining particles together by creating bonds between them. There are several different methods of granulation. The most popular which is used by over70% of formulation in tablet manufacture is wet granulation.

3. FORMULATION OF ENTECAVIR TABLETS BY DIRECT COMPRESSION METHOD

Tablets containing 1 mg of entecavir were prepared by direct compression method. The procedure includes:

Step 1: The drug, superdisintegrant and diluents were passed through sieve no #40. All the above ingredients were co-ground and properly mixed geometrically.

Step 2: Binder also was passed through sieve no #40 and finally added to above mixture blended. Finally magnesium stearate was passed through sieve no# 60, mixed and blended with the initial mixture in poly-bag.

Step 3: The powder blend was compressed into tablets using 7x7.31mm diamond shaped punches to get tablets of 100 mg weight on a 12 station rotary tablet machine (Rimek mini press-1).

Step 4: The formulated tablets were stored in a tightly closed glass containers and evaluated for various characteristics.Then the punched tablets were subjected to coating.

- **Selection of diluents**

Diluent are used to increase the bulk of the formulation. Different diluents were tried for the optimization in the formula of formulation which included in table2. Glidants are used to promote powder flow by reducingin ter particle friction and cohesion. Different glidants including magnesium state,SSG and included in the formula of entecavir tablets for the selection of suitable one.

Lubricants are agents added in small quantities to tablet formulations todecrease friction at the interface between a tablet's surface and the die wall during ejection and reduce wear on punches & dyes.

2. The most suitable lubricant was selected based on the properties of granules including bulk density, tapped bulk density, Carr's index, Hausner's ratio and angle of repose [18].

Table: 3.1 Experimental working formula

S. No	Ingredients	F1	F2	F3	F4	F5	F6	F7
1	Entecavir (mg)	1	1	1	1	1	1	1
2	Lactose (mg)	30	31	32	33	48	43	36
3	MCC (mg)	68	66.5	65	63.5	48	52	60
4	Crospovidone (mg)	-	0.5	1	1.5	2	3	2
5	SSG (mg)	-	-	-	-	-	-	-
6	Magnesium state (mg)	1	1	1	1	1	1	1

Cont….

S. No	Ingredients	F8	F9	F10	F11	F12	F13	F14
1	Entecavir (mg)	1	1	1	1	1	1	1
2	Lactose (mg)	31	32	36	33	40	43	44
3	MCC (mg)	66.5	65	61	63.5	56	52	52
4	Crospovidone (mg)	-	-	-	-	-	-	-
5	SSG (mg)	0.5	1	1	1.5	2	3	2
6	Magnesium state (mg)	1	1	1	1	1	1	1
7	Total weight	100	100	100	100	100	100	100

4.Evaluation of Tablets:

4.BULK DENSITY, COMPRESSIBILITY INDEX, HAUSNER'S RATIO, AND ANGLE OF REPOSE OF ENTECAVIR BLEND

Table: 4.6Flow properties of blends in different formulations

S.No	Formulation code	Density(gm./ml)		Compressibility index	Hausner's ratio	Angle of repose(degrees)
		Bulk	Tapped			
1	F1	0.462	0.539	14.28	1.16	26.56
2	F2	0.469	0.558	15.94	1.18	27.47
3	F3	0.478	0.538	11.15	1.12	27.02
4	F4	0.480	0.546	12.08	1.13	27.92
5	F5	0.464	0.546	15.01	1.17	29.24
6	F6	0.462	0.545	15.22	1.17	27.92
7	F7	0.459	0.539	14.84	1.17	31.38
8	F8	0.480	0.540	11.11	1.12	31.5
9	F9	0.475	0.544	12.68	1.14	31.79
10	F10	0.466	0.540	13.70	1.15	30.96
11	F11	0.475	0.547	13.16	1.15	30.54
12	F12	0.473	0.551	14.15	1.16	30.96
13	F13	0.480	0.552	13.04	1.15	31.38
14	F14	0.472	0.555	14.95	1.17	30.54

Evaluation parameters of uncoated tablets

Formulation code	Evaluation parameter				
	Thickness (mm)	Hardness (KP)	Friability (%)	Average weight variation (n=20)	Disintegration Time (Min)
F1	2.82	5.16	0.467	100.2±0.8	2.11
F2	2.99	5.32	0.466	100.7±1.6	2.45
F3	2.85	5.25	0.525	99.6±1.2	2.00
F4	2.82	4.76	0.458	100.4±0.8	1.52
F5	2.83	5.16	0.393	101.3±1.4	2.05
F6	2.81	4.34	0.528	100.6±1.7	1.53
F7	2.81	4.44	0.520	98.5±1.5	1.28
F8	2.82	5.00	0.400	99.2±2.0	1.50
F9	2.58	5.18	0.286	102.1±0.5	2.00
F10	2.84	5.12	0.423	100.1±0.5	1.59
F11	2.82	5.12	0.530	97.8±1.0	2.00
F12	2.96	4.33	0.436	99.1±1.2	1.42
F13	2.92	4.09	0.545	100.5±1.5	1.52
F14	2.83	4.80	0.526	100.3±0.5	2.00

RESULTS OF *IN-VITRO* RELEASE PROFILE(uncoated tablets)

Table: 4.14 *In-Vitro*drug release profile of formulations F1-F7 (uncoated)

S.No	Time (min)	F1	F2	F3	F4	F5	F6	F7
1	10	62.95	74.04	76.93	84.40	84.74	82.22	84.40
2	20	74.23	82.74	85.13	89.50	89.24	90.12	91.00
3	30	82.90	89.24	90.65	94.60	93.32	96.32	95.58
4	45	88.15	96.01	96.62	97.91	98.18	99.88	98.38

Table: 4.15 *In-Vitro*drug release profile of formulations F8-F14 (uncoated)

S.No	Time (min)	F8	F9	F10	F11	F12	F13	F14
1	10	65.37	77.08	82.60	85.61	84.26	81.43	79.28
2	20	74.01	88.07	87.44	89.91	89.63	89.12	85.54
3	30	83.39	92.24	93.03	95.25	95.21	95.80	92.29
4	45	90.30	95.60	97.15	97.41	97.87	99.60	98.47

4.Discussion:

- Entecavir tablets were formulated by using direct compression method using lactose as diluent, microcrystalline cellulose as binder, crospovidone and sodium starch glycolate as super disintegrant and magnesium stearate as lubricant.

- The drug and excipients compatibility studies were performed by means of physical mixture of drug and excipients under FTIR. The spectral analysis indicated that the drug is compatible with the formulation components.

- The blends were analyzed for precompression parameters like bulk density, tapped density, compressibility index, Hausner's ratio, angle of repose and the results were found to be within the limits.

- Bulk density and tapped density values range between 0.459 to 0.480 gm/cc and 0.538 to 0.558 gm/cc respective and the values are within the limits.

- Compressibility index has been proposed as an indirect measure of bulk density, size, shape, surface area and cohesiveness of materials. Compressibility index values ranges between 11.11 to 15.94.

- Hausner's ratio expresses the relative mechanical compression of blend. With the help of Hausner's ratio attempts can be made at predicting the both extent of compression and flow problems as well.

- Hausner's ratio values range between 1.12-1.18 which fall under good flow range
- Visually examined tablets from each formulation of batch showed proper diamond shaped compressed tablets.
- Hardness of each formulation was analyzed for all the 14 formulations and was found to have good hardness.
- Tablets mean thickness were almost uniform in all the formulations and are found to be in the range of 2.58-2.94mm, for un coated tablets and in the range 3.28-3.35 mm, for coated tablets.
- Friability values are found to be less than 1% in all cases and considered to be satisfactory and the values range between 0.393 and 0.545.
- The total weight of each formulation was not maintained constant however the weight variation of the tablets was within the limits of ± 10 %.
- The prepared tablets were checked for assay as per USP specifications. All the formulations passed the test and the percentage of active ingredient in the un coated tablets ranges from 96.86 to 99.43% and coated tablets range form 96.94-99.77.
- The disintegration times for all the formulations was found to be within the permissible ranges but F7 has exhibited a lower disintegration time for un coated tablets 1.28min and coated tablets disintegration time of 2.26 min.
- The dissolution studies of 14 formulations were carried out in pH 6.8 phosphate buffer and the percentage of drug release was calculated. All the formulations were kept for 45 minutes. It was found that all formulations met the standard limits.
- The dissolution profile of each formulation was compared with that of the innovator product and found that F7 had more similar percentage ofdrug release with that of innovator.
- The similarity and dissimilarity factor obtained for Entecavir was found to be within the standards.
- Final batch was charged for the stability study with packing at 25^0 C/60% RH and 40^0 C/75% RH for two months. The results obtained after the stability period was not having any change than the initial results.

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