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Formulation, evaluation and optimization of granulating agents on the tablets containing poorly water-soluble anti-HIV drug

Manish K. Gupta^{1*}, Avinash Gupta², Vijay Sharma³, Ashutosh Sharma⁴, Praveen Jaiswal⁵

¹School of Pharmaceutical Sciences, Jaipur, National University, Jaipur, Rajasthan, India

²Poddar International College of Pharmacy, Jaipur, Rajasthan, India

³Goenka College of Pharmacy, Lachhmangarh, Sikar, Rajasthan, India

⁴Jaipur College of Pharmacy, Jaipur, Rajasthan, India

⁵Lords University, Alwar, Rajasthan, India

Abstract:

Elvitegravir have low dissolvability in aqueous media. Because of poor aqueous solvency, formulation improvement turns out to be very troublesome as this may reason for inconstancy in percent drug discharge. In such kind of conditions detailing synthesis and interaction have a definitive impact in concluding the % discharge in the dissolution medium. Nonetheless, Commercial products of drug Elvitegravir are accessible yet no work in regards to the formulation perspective is accounted for. In the current study, effect of granulating agent, upon Physico-substance parameter of Elvitegravir drug eventual outcome was contemplated. The medication Elvitegravir goes under class II classification for example low solubilization and poor penetrability. The medication discharge from becomes a rate limiting factor for their absorption. Thus, for advancement of retention of Elvitegravir, its solubilization in the media ought to get enhanced. For increment of Elvitegravir dissolvability and delivery, formulation variables factors assume a huge part. The significant target of this investigation was to assess the formulation variables such as granulating agent, for example, Gum Arabic, Pharma Sugar, PVP, Klucel, Hypromellose, and Paste & Crayogel. According to the observed outcomes granulating agents like Gum Arabic, Paste, Pharma Sugar greatly influence the release of final product. As opposed to end result final product manufactured from pure drug, the products made from these excipients have significant impact on dissolution efficiency.

Keywords:

Granulating Agents, Binders, Solubility, Bioavailability, Drug Release

1. Introduction:

The finished product get disintegrate in the granular form and then further disintegrate into fine particles. Comparatively percentage drug release from granules or intact finished product is slower than the fine particles. So for fast dissolution, disintegrating time is also a major factor. After release of active part in gastrointestinal fluid it will get absorb in the biological fluid after passing through plasma membrane barrier. So drug dissolution become a rate limiting factor or absorption rate controlling factor, in case of molecules having slower drug release. Singh et al.; (2016) deliberate the nanoparticles of the API. The intention of this experiment was to convalesce the Solublization and biological availability of the API i.e. Atorvastatin. Obtained nanoparticles give a much recovered solublization and % release characteristics in comparison to inherent API. Saffari et al. (2016) adsorbed the drug on the porous ingredients like mannitol. The intention of this experiment was to convalesce the Solublization and biological availability of the APIs i.e. Nifedipine and Indomethacin. Jyotsana et al. (2015) deliberate the hydrotropic mixture of the API. The intention of this experiment was to convalesce the Solublization and biological availability of the API i.e. Laurasidone. Widanapathirana et al. (2015) deliberate the copolymers of the API with the vinyl pyrrolidones. The object of this experiment was to convalesce the Solublization and biological availability of the API i.e. phenytoin. Techniques utilized for scheme the formula was adsorbing the API on the polymers. Sun et al. (2015) deliberate a nanosuspension of the API. The intention of this experiment was to convalesce the Solublization and biological availability of the API i.e. itraconazole. Murtaza et al. (2014) deliberate complexes and dispersions of the API. The intention of this experiment was to convalesce the Solublization and biological availability of the API i.e. Furosemide. Techniques utilized for scheme the formula was use of solubility enhancers. Tawfeek et al. (2014) deliberate dispersions of the API.

The intention of this experiment was to convalesce the Solublization and biological availability of the API i.e. Loronoxicam (LOR) drug. Techniques utilized for scheme the formula was co-evaporation and by surface assimilation onto Neusilin. Solubility of some drugs like Phenbutazone (Jain SC. *et al*; 1981), prednisolone (Narurkar AN. *et al*; 1983), tolbutamide (Mortada LM. *et al*; 1982), indomethacin (Monkhouse DC. *et al*; 1972), phenylmethabutazone (Johansen H. *et al*; 1977), was increased by depositing low water soluble drug on the inert excepients.

At the site of action, from the finished product drug permeation in blood circulation will be

impacted by the disintegration of finished product to the fine particles, dissolution of these fine particles in biological fluid, and transportation of active moiety via selective plasma membrane by different drug carrier technology. Drug dissolution is directly related to its absorption (Permeability) and bioavailability. For enhancement of drug dissolution various granulating agents are used.

2. Materials and methods:

Elvitegravir was received as gift sample from M/s Eli Lilly and Company India, Gum Arabic from M/s Loba Chemie, Pharma Sugar, Klucel, Hypromellose, Crayogel, Talcum and Compritol from M/s Arihant Pharma. PVP from M/s BASF, Starch from M/s Roquette India and Lactose M/s DFE PHARMA

2.1. Method for the estimation of elvitegravir:

Different concentration solution of Elvitegravir was manufactured in different media. After the scanning in the UV Spectroscopy maximum absorbance was reported in the diluted (N/10) HCl. Highest absorbance reported at the λ of 313 nm (Veera V. et al; 2011).

2.2. Standard media:

As the drug is soluble in non-aqueous media, hence 0.1% w/w standard medium of Elvitegravir was manufactured by dissolving it in Methanol solvent.

2.3. Procedure:

Different concentration of Elvitegravir i.e. 5×10^{-6} gm/ ml, 10×10^{-6} gm/ ml, 15×10^{-6} gm/ml, 20×10^{-6} gm/ ml and 25×10^{-6} gm/ ml, were manufactured by diluting the Standard media of Elvitegravir with the required quantity of N/10 HCl. Test solutions were scanned in spectroscopy at the λ of 313 nm using diluent N/10 HCl as a blank.

2.4. Manufacturing of elvitegravir tablets:

For the manufacturing of Elvitegravir Unit Dosage Form multiple types of granulating or binding agent were used. For granule formation aqueous process was utilized according to formula of table 1.0.

2.5. Procedure:

All components are weighed accurately, as per the composition of Table. 3.3 and labeled properly. Drug Elvitegravir, Lactose and MCC were added together in a SS container and passed thru mesh no. 20. According to the formulation particular granulating or binding agent taken and prepared a granulating solution by addition and mixing the granulator in the de ionized water. Stir the solution properly to completely dissolve the granulating agent. Then granulating agent transferred to the powder mix of API uniformly and mixed. This wetted mixture dried at 60°C for 35 min to obtain the semidried mixture. This mixture passed thru mess 12 to find the desired granular size. If require these granules were further dried to accomplish the wanted water content. These semi dried granules further dried for 1 hr. and passed thru mess 20. Thereafter, these granules were added with lubricants properly to attain the uniform final blend.

Final blend was taken for making of unit dosage form keeping the desired physical parameter.

3. Physicochemical parameters of tablets:

3.1. Assay:

Collect the 10 units of dosage form and crushed in the pastle mortar. Sample qty. of powder similar to the dose of drug taken. This sample quantity was treated with methyl alcohol several times to dissolve out the Elvitegravir in methanol. This solution was filtered with whatmann filter paper. This drug solution was further diluted with the dissolution media of N/10 HCl. The qty. of Elvitegravir in the solution was calculated using spectroscopy at λ of 313 nm. Standard curve was utilized for the quantification of Elvitegravir in the solution.

3.2. Tablet strength:

Strength of unit dosage form was measured by Dr. Sheluinger tablet strength analyzer.

3.3. Friability:

Fragility of unit dosage form was measured by the apparatus of M/s Elecrolab India.

3.4. Disintegration time:

Erosion or de-aggregation in the unit dosage form was measured by DT apparatus of M/s Elecrolab India.

3.5. Drug release:

Drug release of Elvitegravir was studied in Eleclrolab Dissolution Equipment. For the dissolution following parameters were kept Apparatus: USP Type II (Paddle) Media: N/10 hydrochloric acid Volume: 0.9 Litre RPM: 50 Temperature of Media: 37°C ± 1°C Sample Volume: 5 ml One unit of tablet was dropped in the each basket of Dissolution Equipment. At the defined time interval sample quantity taken and treated with the dissolution solution. After proper dilution and treatment the sample was run in the spectroscopy at the λ of 313 nm. Quantification of drug amount in the sample was carried using standard curve. The test was proceeded in triplicate (n=3).

Table. 1: Manufacturing Formula of Different Granulating Agent

<i>Composition</i>							
<i>Component</i>	<i>E1 (Qty/tab.)</i>	<i>E2 (Qty/tab.)</i>	<i>E3 (Qty/tab.)</i>	<i>E4 (Qty/tab.)</i>	<i>E5 (Qty/tab.)</i>	<i>E6 (Qty/tab.)</i>	<i>E7 (Qty/tab.)</i>
Elvitegravir	100.00 mg	100.00 mg	100.00 mg	100.00 mg	100.00 mg	100.00 mg	100.00 mg
Gum Arabic	4.00 mg	0.00	0.00	0.00	0.00	0.00	0.00
Pharma Sugar	0.00	4.00 mg	0.00	0.00	0.00	0.00	0.00
PVP	0.00	0.00	4.00 mg	0.00	0.00	0.00	0.00
Klucel	0.00	0.00	0.00	4.00 mg	0.00	0.00	0.00
Hypromellose	0.00	0.00	0.00	0.00	4.00 mg	0.00	0.00
Paste	0.00	0.00	0.00	0.00	0.00	4.00 mg	0.00
Crayogel	0.00	0.00	0.00	0.00	0.00	0.00	4.00 mg
MCC	43.00 mg	43.00 mg	43.00 mg	43.00 mg	43.00 mg	43.00 mg	43.00 mg
Talcum	2.00 mg	2.00 mg	2.00 mg	2.00 mg	2.00 mg	2.00 mg	2.00 mg

Compritol	3.00 mg	3.00 mg	3.00 mg	3.00 mg	3.00 mg	3.00 mg	3.00 mg
Lactose up to	200.00 mg	200.00 mg	200.00 mg	200.00 mg	200.00 mg	200.00 mg	200.00 mg

4. Results:

4.1. Standard graph:

For the quantification of Elvitegravir a standard graph in N/10 HCl at the λ_{max} 313 nm was plotted. The observed absorbances at various concentrations of Elvitegravir are mentioned in Table. 2.0.

Table. 2: Standard Graph of Elvitegravir

<i>Concⁿ</i>	<i>Abso.</i>
5 $\mu\text{g/ml}$	0.151
10 $\mu\text{g/ml}$	0.295
15 $\mu\text{g/ml}$	0.427
20 $\mu\text{g/ml}$	0.594
25 $\mu\text{g/ml}$	0.745

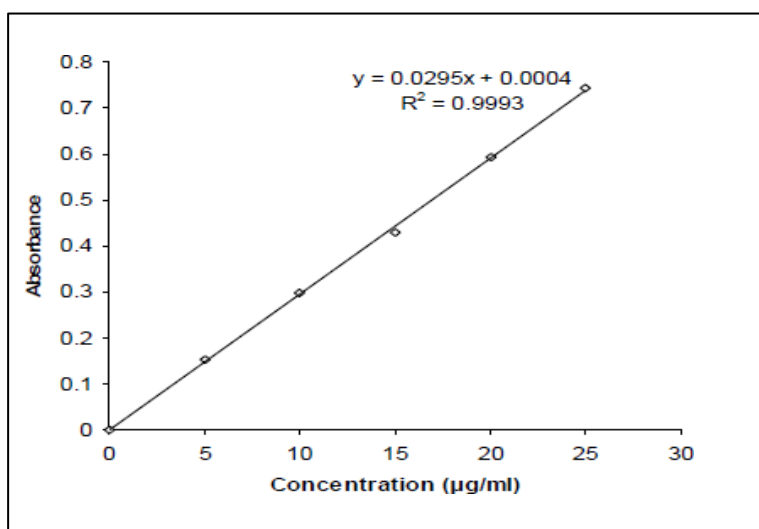


Figure. 1: Calibration Curve of Elvitegravir

According to the observation, at the given drug concentration range, this method follows the Beer's law. Hence this method can be utilized for the invitro drug dissolution study.

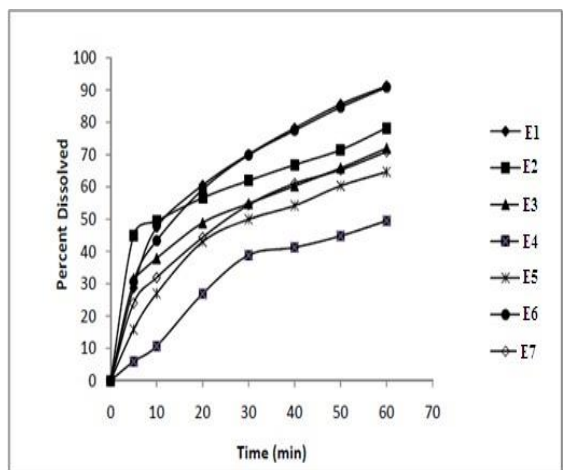
4.2. Evaluation of tablets:

Table. 3: Physical Parameters of Tablets Manufactured with Multiple Granulating Agents

Compositio n	Assay	Tablet Strength	Friabilit y	DT
E 1	100.8 mg	4 – 6 Kp	0.45 %	2.5 min
E 2	100.3 mg	7 – 6 Kp	0.76 %	0.7 min
E 3	100.2 mg	4.3 – 5.0 Kp	0.53 %	2.0 min
E 4	99.7 mg	11 – 12 Kp	0.20 %	18.0 min
E 5	99.4 mg	11 – 12 Kp	0.18 %	16.0 min
E 6	100.1 mg	4.5 – 5.5 Kp	0.45 %	1.1 min
E 7	99.6 mg	4.5 – 5.5 Kp	0.10 %	1.0 min

Table. 4: Drug Release of Tablets Manufactured with Multiple Granulating Agents

Time	% Release ($X \pm SD$)						
	E 1	E 2	E 3	E 4	E 5	E 6	E 7
5 min	28.65 % \pm 1.20	44.41 % \pm 1.30	32.10 % \pm 1.50	5.95 % \pm 0.95	15.81 % \pm 0.95	30.61 % \pm 1.30	23.91 % \pm 1.10



10 min	48.31 % ± 1.40	49.10 % ± 1.20	37.90 % ± 1.20	10.71 % ± 1.10	27.05 % ± 1.40	43.21 % ± 1.10	31.70 % ± 1.20
20 min	61.20 % ± 1.50	57.10 % ± 1.20	48.81 % ± 1.10	26.91 % ± 0.93	43.01 % ± 1.10	59.21 % ± 1.40	44.30 % ± 1.20
30 min	69.78 % ± 1.10	61.80 % ± 1.40	54.90 % ± 0.93	38.80 % ± 1.40	49.91 % ± 1.30	69.81 % ± 0.95	54.41 % ± 1.40
40 min	78.50 % ± 0.95	66.90 % ± 1.10	60.80 % ± 1.40	41.32 % ± 1.10	54.10 % ± 1.10	28.65 % ± 0.93	61.15 % ± 0.95
50 min	86.20 % ± 1.60	71.70 % ± 0.94	65.85 % ± 1.20	44.75 % ± 1.30	60.28 % ± 0.96	28.65 % ± 1.30	65.20 % ± 1.10
60 min	91.40 % ± 1.40	78.30 % ± 1.30	71.80 % ± 1.10	49.48 % ± 1.10	64.61 % ± 1.10	28.65 % ± 1.20	70.81 % ± 1.40

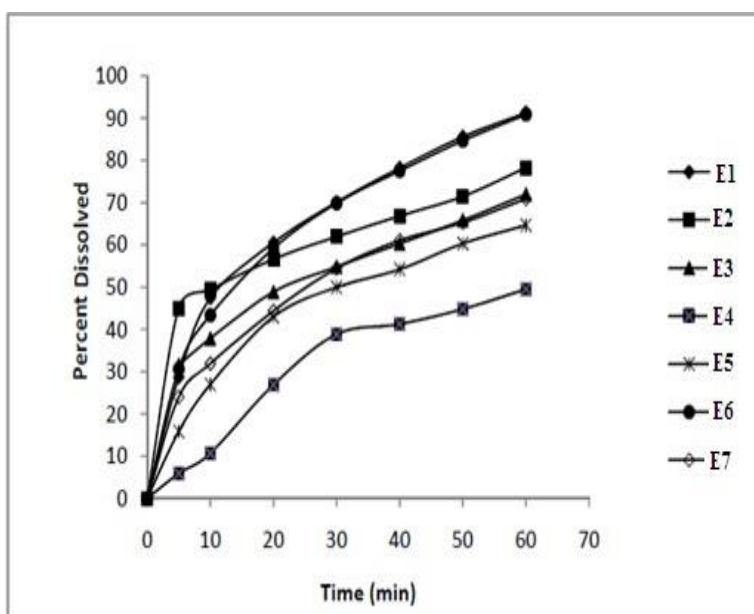


Figure. 2: Release of Tablets Manufactured with Multiple Granulators

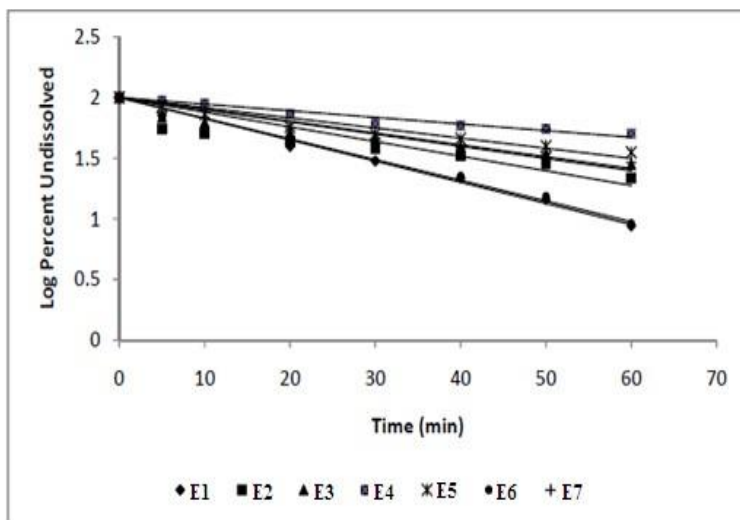


Figure. 3: Logarithmic Release of Tablets Manufactured with Multiple Granulating Agents

Table. 5: Values of (r) according to Zero order and first order Kinetics

Composition	r value	
	Zero order kinetics	First order kinetics
E 1	0.9192	0.9751
E 2	0.9904	0.9974
E 3	0.9761	0.9881
E 4	0.9943	0.9935
E 5	0.9531	0.9746
E 6	0.9741	0.9971
E 7	0.9931	0.9995

According to the observed results physical parameters of the Final product were satisfactory and accord to the Pharmacopoeial requirement. However, Composition E4 & E5 doesn't qualify the DT test as per pharmacopoeia limit of NMT 15 min.

Release data for all compositions were varying according to the type of granulating agent used. The enhanced drug release performance of different binders are as Gum Arabic > Pharma Sugar > PVP > Crayogel > Hypromellose > Klucel. These compositions qualify the Pharmacopoeial & GMP requirements of finished product.

Hence, the compositions having the granulating agent Gum Arabic, starch and Pharma Sugar were carried forward for development of Elvitegravir final product.

Values of (r) according to Zero order and First order Kinetics is mentioned in the Table. 5.0. As per the observed data release of Elvitegravir looking to be best fitted in first order because of their higher values.

5. Conclusion:

From the observed results following conclusions are made.

1. Physicochemical parameters and release of final products are majorly determined by the Granulating Agents.
2. Increased release of different granulating agents are Gum Arabic > paste > Pharma Sugar > PVP > Crayogel > Hypromellose > Klucel.
3. Finished products manufactured using the granulating agents of Gum Arabic, Paste and Pharma Sugar qualifies the Pharmacopoeial & GMP requirements of compressed tablets.

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