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FORMULATION DEVELOPMENT AND EVALUATION OF IMMEDIATE RELEASE TABLETS OF SYNTHETIC GLUCOCORTICOID USING VARIOUS DISINTEGRANT AND THEIR EFFECT ON DISSOLUTION OF DRUG PRODUCT

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ABSTRACT

The present study was aimed to formulate, develop and evaluate the immediate release tablet of synthetic glucocorticoid using various disintegrants and to observe the dissolution profile of drug product. The different disintegrant used like a partially gelatinized starch, sodium starch glycolate, crosscarmellose sodium in various concentration to achieve the drug release profile compare to RLD product. The super disintegrants like partially gelatinized starch, sodium starch glycolate, crosscarmellose sodium which shows different mechanism of action to disintegrate the tablet. So, for good dissolution profile as compare with RLD product we use various disintegrants at different concentration.

The generic tablet of dexamethasone 6mg was prepared by considering the approved reference product in Europe. The tablet was prepared by direct compression method. The excipient was used is based on the excipient which is used in reference listed product. Regarding a dissolution time we can prepare 6 optimized batches by OFAT drug design changing a concentration of disintegrant also a different disintegrants which shows the different dissolution profile and select the proper composition.

Keywords: Dexamethasone, synthetic glucocorticoids, disintegrants, dissolution profile

INTRODUCTION

The oral route of dose administration is most widely used due to ease of administration and most convenient route. Also, the oral route shows the more patient

compliance. The immediate drug delivery systems give the rapid disintegration of the tablet and give the fast dissolution drug profile **[1]**.

Dexamethasone is a synthetic glucocorticoid which is primarily used for anti-inflammatory effects and immuno-suppressant in disorders of many organ systems. It was tested in hospitalized patients with COVID-19 in United Kingdom's national clinical trial recovery and was found to have benefits for critically ill patients. According to primary findings shared with WHO, for patients on ventilators, the treatment was shown to reduce transience by about one-third, and for patients requiring only oxygen, transience was cut by about one- fifth. Dexamethasone Tablets USP were approved in Europeprior to 1980 for the treatment of allergic states, dermatological diseases, endocrine disorders, gastrointestinal diseases, hematologic disorders, neoplastic diseases, nervous system, ophthalmic diseases, renal diseases, respiratory diseases, rheumatic disorders. Product was also approved for many miscellaneous uses like diagnostic testing of adrenocortical hyperfunction, trichinosis with neurologic or myocardial involvement, tuberculous meningitis with the subarachnoid block or impending block when used with appropriate antituberculous chemotherapy **[2, 3]**.

The generic Dexamethasone Tablets USP, 6 mg was developed considering the approved reference product in Europe. The generic formulation is solid, oral dosage form of Dexamethasone Tablets USP, 6 mg prepared by direct compression method. Dexamethasone has high solubility across physiological pH range and classified as BCS class I/III (high solubility; high/low permeability) drug substance. Finer particle size (D_{90}<7μm) of drug substance was selected to achieve content uniformity and dissolution of drug product considering low dose formulation. Excipients chosen for development were based on excipients used in the reference product **[4-6]**.

MATERIAL AND METHODS

Dexamethasone USP was obtained as a gift sample from Enaltec Pharma Research Pvt. Ltd., Mumbai and the excipients used in the formulation development study such as microcrystalline cellulose, lactose monohydrate, partially pregelatinized starch, sodium starch glycolate, croscarmellose sodium, magnesium stearate, etc. were of pharmaceutical grade.

Experimental work:

Immediate release tablets of Dexamethasone Tablets USP, 6 mg were prepared by direct compression method as per the formulation details given in **Table**

1. Following manufacturing method was used to prepare the tablets of Dexamethasone Tablets;

a. All the ingredients were dispensed in individual polybag using calibrated balance.
b. All the ingredients were sifted through 40 mesh except FD&C Green No.3 and magnesium stearate. FD&C Green No. 3 was sifted through 200 mesh and magnesium stearate was sifted through 60 mesh.
c. Lactose monohydrate and microcrystalline cellulose were added in rapid mixer granulator (RMG) and mixed for 5 min. at slow impeller speed.
d. FD&C Green No. 3 was dispersed in specified quantity of purified water under stirring.
e. Blend of step c was granulated using dispersion of step d at slow impeller speed.
f. The granulated blend of step e was dried in rapid dryer to remove the excess water and to achieve uniform distribution of colorant in the blend.
g. Blend of step f and remaining excipients except magnesium stearate were added in suitable blender and mixed for 15 min. at 12 RPM to achieve uniform distribution of drug substance throughout the blend.
h. Magnesium stearate of step b was added in the blender of step g and mixed for 5 min at 12 RPM.
i. The lubricated blend of step h was compressed on rotary press using 'B' tooling 6.30 mm round and concave punches.

Table 1: Formulation table for Dexamethasone tablet 6mg

Batch No.		F_1	F_2	F_3	F_4	F_5	F_6
Batch Details		Bach with partially pregelatinized starch as disintegrant	Bach with 10% sodium starch glycolate as disintegrant	Batch with 8% croscarmellose sodium as disintegrant	Batch with 9% croscarmellose sodium as disintegrant	Batch with 10% croscarmellose sodium as disintegrant	Batch with finer PSD of drug substance (D_{90} – 6.93 µm)
Sr. No.	Ingredients	mg/tablet					
1.	Dexamethasone	6.00	6.00	6.00	6.00	6.00	6.00
2.	Lactose monohydrate	32.95	37.95	39.95	38.95	37.95	37.95
3.	Microcrystalline cellulose	34.00	34.00	34.00	34.00	34.00	34.00
4.	Sucrose	10.00	10.00	10.00	10.00	10.00	10.00
5.	Partially pregelatinized starch	15.00	-	-	-	-	-
6.	Sodium starch	-	10.00	-	-	-	-

	glycolate						
7.	**Croscarmellose sodium**	**-**	**-**	**8.00**	**9.00**	**10.00**	**10.00**
8.	**FD&C Green No. 3**	**0.05**	**0.05**	**0.05**	**0.05**	**0.05**	**0.05**
9.	**Magnesium stearate**	**2.00**	**2.00**	**2.00**	**2.00**	**2.00**	**2.00**
10.	**Purified water**	**q.s.**	**q.s.**	**q.s.**	**q.s.**	**q.s.**	**q.s.**
Total weight (g)		**100.00**	**100.00**	**100.00**	**100.00**	**100.00**	**100.00**

Preformulation study:

1. **Melting point**:

   The melting point of the given API was determined by using capillary method **[7]**.

2. **Solubility determination**:

   The solubility analysis of the given drug was carried out by 10 mg of the drug is dissolved in 10 ml of the given solvent like water, ethanol, methanol, chloroform **[8]**.

3. **Compatibility study**:

   This study used for the identification of drug substance also to check out the compatibility with other excipient. In this we compare the peak obtained with each excipient peak **[9]**.

4. **UV- Spectrophotometric method:**

   This study generally used for the identification of the drug product.1 mg drug can dissolved in 100 ml methanol to prepare a stock solution. Further, from above solution 1 ml can pipette out and dilute up to 100 ml by water to prepare 100 ppm solution. Also, 1 ml pipette out from above solution and dilute up to 100 ml to prepare 10 ppm solution. This 10 ppm dilution is a scan at UV software. By scanning this dilution, we can obtain 243 nm wavelength **[10]**.

Physical evaluation of formulation blend:

1. **Bulk density:**

   A bulk density was determined by introducing the measured amount of powdered blend into the measuring cylinder and visually observes the bulk volume in measuring cylinder **[11]**. The bulk density was calculated by the following formula,

   Bulk Density (B.D.) $=\frac{mass}{bulk\ volume}$

2. **Tapped density:**

   The tapped density was determined by using the Electrolab tap density tester apparatus (USP I). In that apparatus the measured amount of powder blend was transferred into the measuring cylinder and tapped up to 10, 500, 1250 taps respectively and measured the tapped tensity by following formula,

Tapped Density (T.D.) $= \frac{mass}{tapped\ volume}$

3. **Hausner's Ratio:**

Hausner's Ratio was determined by calculating the ratio of tapped density to the bulk density **[12]**. It is the generally used for to observe the flow property of powder blend. It was calculated by the following formula.

Hausner's ratio= $\frac{tapped\ density}{bulk\ density}$

The value of Hausner's ratio between the 1.05 – 1.18 which indicate the good flow property of powder blend.

4. **Compressibility Index:**

It was calculated by following formula.

Compressibility Index = $\frac{tapped\ density - b\quad density}{tapped\ density} \times 100$

The value of compressibility index between the 5–15 which indicates the good flow property **[13]**.

5. **Loss on drying (LOD):**

This parameter generally used to check the moisture content present in the lubricated blend. Due to the presence of the moisture in blend it affects the flow property of powder and gives the weight variation of tablets during compression. It must be less than 3 %w/w **[14]**.

In-process parameter during compression:

1. **Tablets weight (mg):**

Take a randomly 10 tablets during a compression and take weight of tablets individually and also 10 tablets at a time to take average weight of tablets.

2. **Thickness:**

Take 10 tablets randomly during compression and thickness was measured by using Vernier caliper scale to calculate the accurate measurement.

3. **Diameter:**

Tablets were selected randomly in-process of compression and measured the tablet diameter by using the Vernier caliper. It should be giving the accurate measurement.

4. **Hardness:**

Take 10 tablets of each formulation during compression by using a Dr. schleuniger apparatus. The hardness of immediate release tablet was lie between the 3 to 5 N for better disintegration also for good dissolution profile.

5. **Disintegration time:**

Disintegration test was carried out on six tablets. The tablets are placed in USP II (paddle) apparatus

[Electrolab Apparatus]. The test was carried out in 900 ml water at 37°C±0.5°C until the complete tablets were not disintegrated. The time for disintegration is measured in seconds.

6. **Friability:**

Take a 6.5 gm weight of tablets and placed into the Roche friabilator apparatus at 25 rpm upto 100 revolution. The friction and shock treatment are given to check the tablet strength. To measure the powder loss of tablets, take a final weight of tablet. Friability was calculated by following formula.

Friability

$$= \frac{initial\ weight - final\ weigh}{initial\ wig} \times 100$$

The value of friability should be not more than 1.0% w/w.

7. **In- vitro drug release study:**

In vitro drug release was carried out using the USP II (paddle) apparatus [Electrolab] in 900 ml of dilute HCl (1ml in 100 ml) solution. The 5-ml sample solution was withdrawn at 5, 10, 15, 20, 30, 45, 60 min. The sink condition was maintained by dissolution media. The given sample was analyzed by RP-HPLC method and percent drug release was calculated **[15]**.

RESULTS AND DISCUSSION

In the given study, immediate release tablet of Dexamethasone was prepared by using the super disintegrants like croscarmellose sodium, pregelatinized starch, sodium starch glycolate at variant concentration. These 6 formulations were prepared by direct compression method. The given formulation was evaluated for the following parameter and results are given in following tables:

1. **Preformulation study:**
   a) **Melting point:** It was observe at 255°C – 264°C
   b) **Solubility: (Table 2)**
   c) **Identification of absorbance maxima: (Figure 1)**
   d) **Compatibility study:**

2) Pre-compression evaluation:

The micrometrics parameter such as bulk density, tapped density, Hausner's ratio, compressibility index, LOD of dexamethasone 6 mg immediate release tablet blend were evaluated. The results are shows in **Table 2.**

3) In-process parameter:

The prepared tablet of dexamethasone were evaluated by various parameters like disintegration time, hardness, thickness, weight variation, friability, % dug release of each batch of tablet. All these parameter

were compared with the RLD product. The results are shows in **Table 4**.

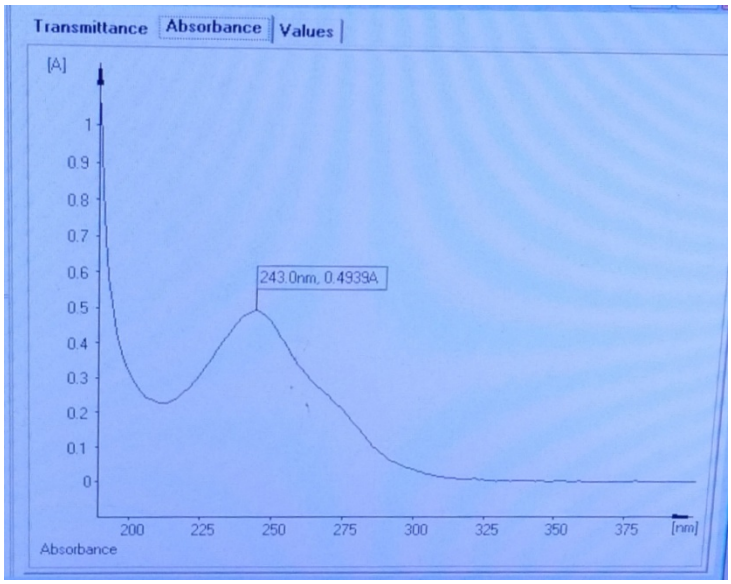
In vitro dissolution profile of formulation:

Comparative dissolution profiles of Reference product and Test products of Dexamethasone Tablets USP, 6 mg in dilute HCl (1 in 100 mL) medium **(Table 5)**.

Graphical representation of comparative dissolution profile of Reference product and Test products of Dexamethasone Tablets USP, 6 mg in dilute HCl (1 in 100 mL) medium **(Figure 3)**.

Table 2: Solubility of Dexamethason

Sr. no.	Organic solvents	Observation
1	Water	Sparingly soluble
2	Ethanol	Soluble
3	DMSO	Soluble
4	Dimethyl formamide	soluble



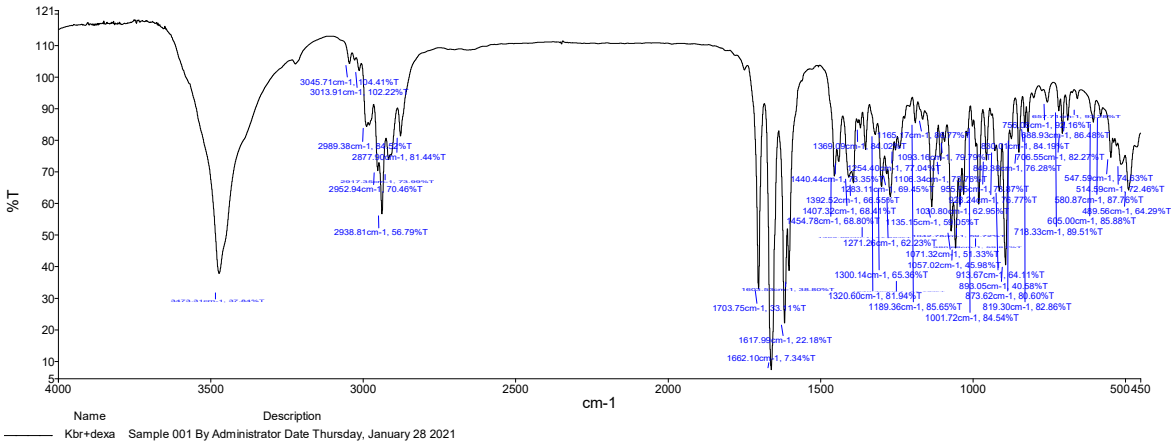


Figure 1: FTIR of pure drug

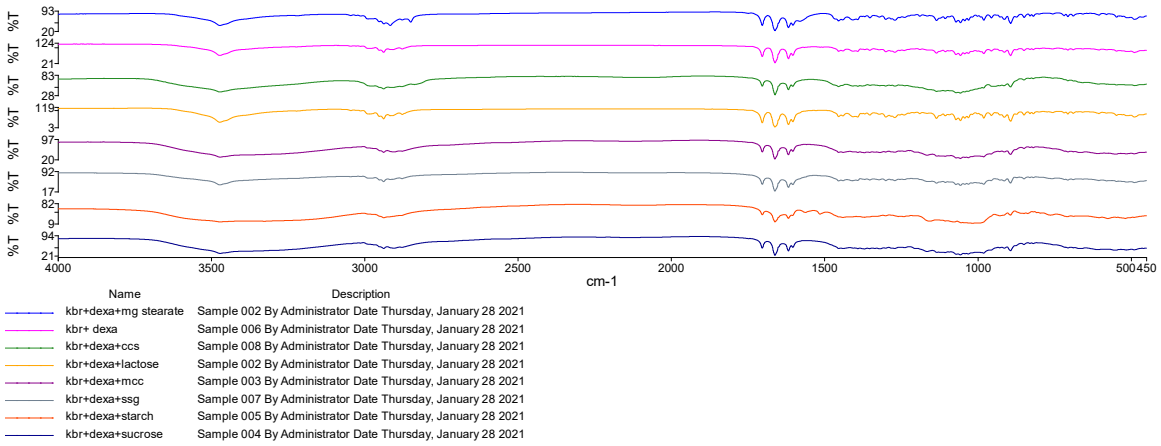


Figure 2: FTIR of drug along with excipient

Table 3: Evaluation of lubricated blend

Sr. No.	Parameter	F_1	F_2	F_3	F_4	F_5	F_6
1.	Bulk Density (gm/ml)	0.62	0.59	0.56	0.62	0.63	0.57
2.	Tapped Density (gm/ml)	0.74	0.77	0.79	0.75	0.72	0.69
3.	Hausner's ratio	1.19	1.31	1.41	1.21	1.17	1.21
4.	Compressibility index	16.22	23.38	29.11	17.33	14.86	17.39
5.	LOD (%w/w)	1.65	1.88	2.13	1.75	1.87	1.59

Table 4: Evaluation of In- process parameter during compression

Sr. No.	Parameter	F_1	F_2	F_3	F_4	F_5	F_6
1.	Appearance	Aqua green colored, round shaped tablets, debossed with"1"above the score line on one side and "MIL" on other side.					
2.	Tablet weight (mg)	101.2-105.7	98.8-101.6	97.9-102.2	99.1-104.4	98.6-103.6	99.7-104.8
3.	Hardness (N)	44-53	42-57	45-55	45-52	47-58	45-54
4.	Thickness (mm)	2.74-2.77	2.62-2.66	2.53-2.56	2.56-2.59	2.52-2.61	2.55-2.61
5.	Diameter (mm)	6.31-6.33	6.30-6.32	6.30-6.32	6.30-6.33	6.29-6.32	6.29-6.31
6.	Friability (NMT 1%)	0.02	0.04	0.12	0.08	0.09	0.09
7.	Disintegration time (min)	35-42 sec.	1-2 min.	1-2 min.	50-82 sec.	35-50 sec.	30-65 sec.

Table 5: In-vitro dissolution profile

Dissolution (%)							
Batch No.	Reference product	F_1	F_2	F_3	F_4	F_5	F_6
Batch details		Test products					
Dissolution condition	USP I (Basket) / 500 mL dilute HCl (1 in 100 mL) / 100 mL						
Time (min.)	% Drug release						
5	82	52	62	70	76	80	78
10	95	67	77	82	89	92	89
15	96	82	83	94	96	96	94
30	96	94	90	95	97	97	98
45	97	98	98	96	99	99	98

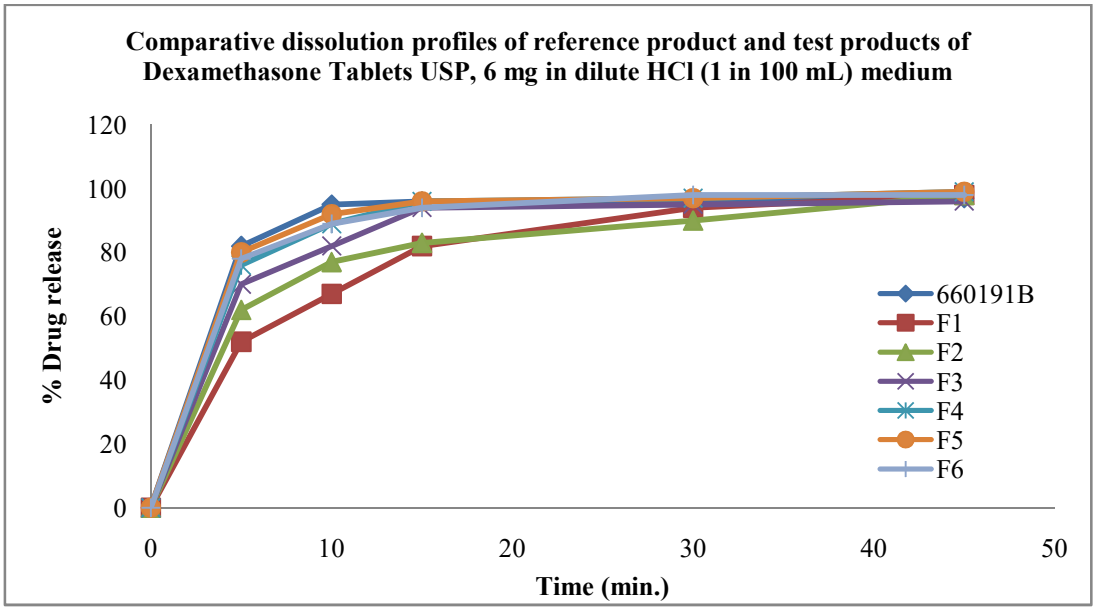


Figure 3

Table 6

Time (min)	Cumulative drug release %	% drug remaining	Square root time	Log cumulative % drug remaining	Log time	Log cumulative % drug release	% drug release	Cube root of % drug remaining	$W_0 - W_t$
0	0	100	0.000	2.000	0.000	0.000	100	4.642	0.000
5	80	20	2.236	1.301	0.699	1.903	80	2.714	1.928
10	92	8	3.162	0.903	1.000	1.964	12	2.000	2.642
15	96	4	3.873	0.602	1.176	1.982	4	1.587	3.055
30	97	3	5.477	0.477	1.477	1.987	1	1.442	3.200
45	99	1	6.708	0.000	1.653	1.996	2	1.000	3.642

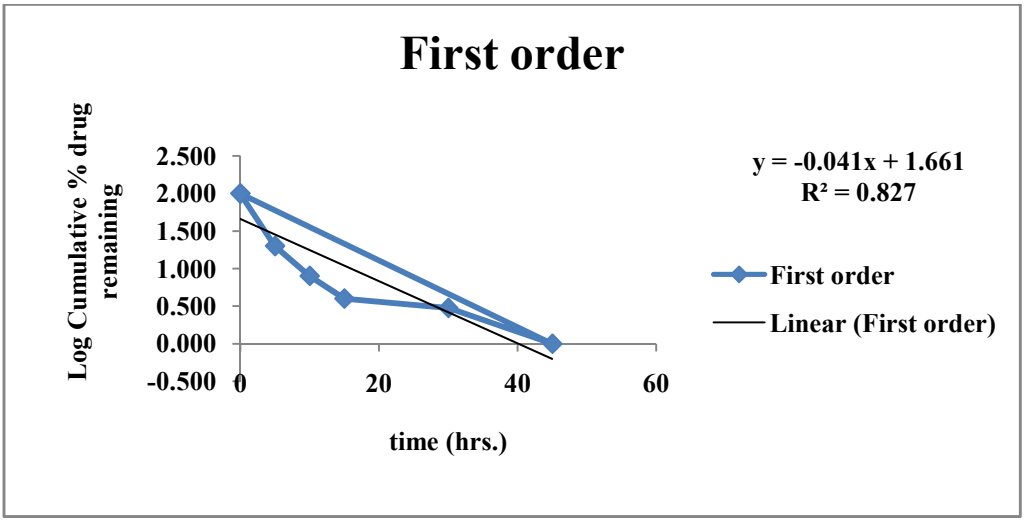


Figure 4

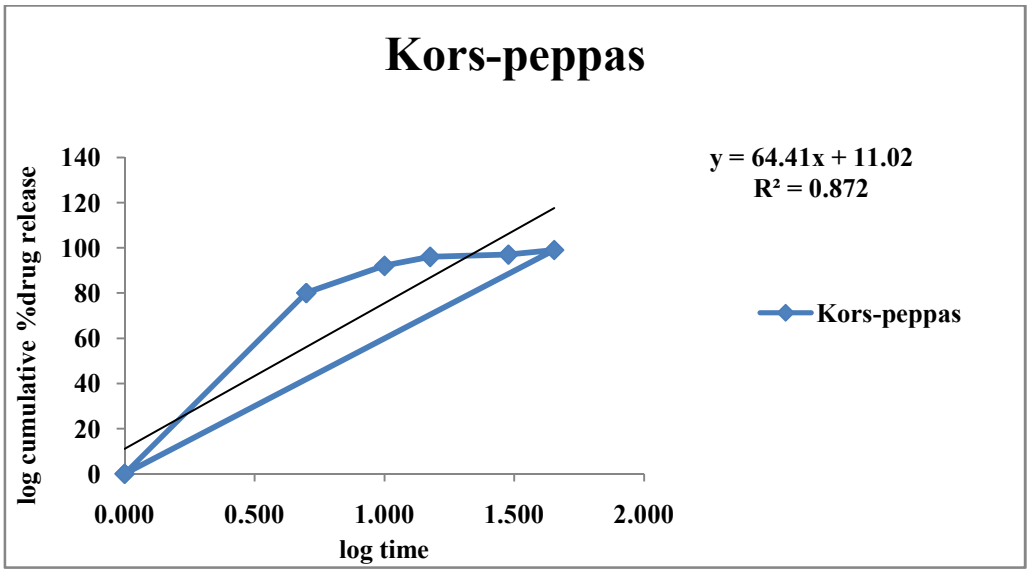


Figure 5

CONCLUSION

The present investigation of this work "formulation development and evaluation of immediate release tablet of synthetic glucocorticoid usingvarious disintegrants and their effect on dissolution drug product" were developed to study dissolution profile of various disintegrants by changing their concentration as compare with RLD product. In summary it is concluded that the given formulation of dexamethasone tablet gives the satisfactory results and by the use of superdisintegrant we achieved the immediate release tablet as compare with RLD. Dexamethasone tablet 6mg were prepared by a direct compression method by using various superdisintegrants like partially gelatinized starch, sodium starch glycolate, crosscarmellose sodium. For this study we can take 3 trial batches by various disintegrants in that F3 batch found to be satisfactory with RLD. Later, we change the conc. of crosscarmellose sodium in formula and taken the trial batches. The F5 batch was found to be a optimize batch. The batch no. F6 shows the smaller API size less than 7 micrometer which gives the good content uniformity and also shows better results compare with other batches and within a limit which shows in the above tables.

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