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Research

Formulation and invitro evaluation of phenytoin orally disintegrating tablet by using direct compression method

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Abstract

An Orally disintegrating tablet disperses readily in saliva and the drug is available in solution or suspension form for the immediate absorption and resulting in rapid onset of action. In the present research work Phenytoin Oral disintegrating tablets were prepared by Direct Compression Technique using varying concentrations of Lycoat, Croscarmellose sodium and Ludiflash as super disintegrants. The formulations prepared were evaluated for precompression & post compression parameters. Form the drug excipient compatibility studies we observe that there are no interactions between the pure drug (Phenytoin) and optimized formulation (Phenytoin+ excipients) which indicates there are no physical changes. Post compression parameters was found to be within the limits. Among the formulation prepared the tablet containing concentration of Ludiflash shows 98.85±1.46% of the drug release within 60 min & follows first order kinetics. The overall result indicated that the formulation F12 containing Ludiflash is better and fulfilling of the needs of the Orally disintegrating tablet.

Keywords: Orally disintegrating tablets, Direct Compression Technique, Phenytoin, Ludiflash, FTIR.

INTRODUCTION

There is an increase in demand for more patient-friendly dosage forms during the last decade. Pharmaceutical technologists have developed a novel oral dosage form called as Orally Disintegrating Tablets (ODTs) that dissolve fast in saliva, usually in a matter of seconds, without the requirement to consume it with water. The rate of drug dissolution and absorption, as well as the beginning of clinical action and drug bioavailability, may be much faster

with ODTs than with traditional dosage forms.

Regulatory agencies have also approved a variety of medications for ODT formulations. In the guidance for industry document "Size, Shape, and Other Physical Attributed of Generic Tablets and Capsules" published by CDER, US FDA, it is recommended that drug manufacturers develop quality target product profiles (QTPPs) for drug candidates. For ODTs, parameters such as disintegration time and tablet size are key components of QTPPs.

Drug Profile

Phenytoin[1]: Phenytoin is an anticonvulsant drug used in the prophylaxis and control of various types of seizures.

Structure:

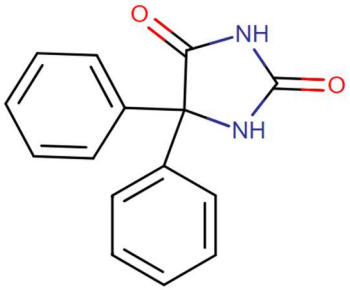

Fig 1: Structure of Phenytoin

IUPAC Name: 5,5-diphenylimidazolidine-2,4-dione

CAS Number: 57-41-0

Molecular Weight: Average: 252.268

Monoisotopic: 252.089877638

Molecular Formula: $C_{15}H_{12}N_2O_2$

Indication

Phenytoin is indicated to treat grand mal seizures, complex partial seizures, and to prevent and treat seizures during or following neurosurgery.

Mechanism of Action

Phenytoin is often described as a non-specific sodium channel blocker and targets almost all voltage-gated sodium channel subtypes. More specifically, phenytoin prevents seizures by inhibiting the positive feedback loop that results in neuronal propagation of high frequency action potentials.

Toxicological effect

Phenytoin toxicity most often affects the cardiovascular and nervous systems. The most common presentation of toxicity depends on the route of administration. Cardiovascular adverse effects are most commonly linked to intravenous phenytoin administration, whereas neurological adverse effects are more common with oral phenytoin administration.

Half life

Oral administration: The half-life of phenytoin ranges from 7 to 42 hours, and is 22 hours on average

MATERIALS AND METHODS

Table 1: Materials used

S. No	Materials	Company
1.	Phenytoin	JOSHI PHARMA Pvt. Ltd
2.	Ludiflash	Signet Chemical Corp., Mumbai
3.	Croscarmellose sodium	Signet Chemical Corp., Mumbai
4.	Lycoat	Signet Chemical Corp., Mumbai
5.	Aspartame	Signet Chemical Corp., Mumbai
6	MCC	Aurbindo Pharma Ltd., Hyd.
7.	Mannitol	Signet Chemical Corp., Mumbai
9	Talc	S.D. Fine Chem. Ltd.
10.	Magnesium stearate	S.D. Fine Chem. Ltd.

Table 2: Instruments & Equipments used

S. No	Instruments/Equipment's	Company
1.	Digital balance	Sartorious Ltd.
2.	Hardness tester	Monsanto
3.	Friability test apparatus	Electrolab USP EF_2
5.	Vernier caliper	Pico India Ltd
6.	Tablet dissolution tester (USPXX IV)	Lab India DS 8000
7.	Disintegration test Apparatus	Electrolab USP Disintegration test apparatus
8.	Tap density tester	K.E.India
9.	UV Spectrophotometer	Single Beam Spectrophotometer (YIS-294)
10.	FTIR Spectrophotometer	Shimadzu -8400 S

Pre formualtion studies[2-5]

Solubility

Solubility of Phenytoin was determined in pH 1.2, pH 7.4, pH 6.4 and 6.8 phosphate buffers. Solubility studies were performed by taking excess amount of Phenytoin in beakers containing the solvents. The mixtures were shaken for 24 hrs at regular intervals. The solutions were filtered by using whattmann's filter paper grade no.41. The filtered solutions are analyzed by spectrophotometrically.

Determination of λ_{max}

10 mg of Phenytoin was dissolved in 10 ml of 6.8 pH Phosphate Buffer by slight shaking (1000 µg/ml). 1 ml of this solution was taken and made up to 10 ml with 6.8 pH Phosphate Buffer, which gives 100 µg/ml concentration (stock solution). From this Stock solution (100µg/ml) pipette out 1ml to 10ml volumetric flask and makeup with 6.8 pH Phosphate Buffer up to 10ml was prepared in 6.8 pH Phosphate Buffer. This solution was appropriately diluted with 6.8 pH Phosphate Buffer to obtain a concentration of 10µg/ml. The resultant solution was scanned in range of 200-400nm on Single beam spectrophotometer (YIS-294).

Calibration Curve for Phenytoin In 6.8 pH Phosphate Buffer

Preparation of Standard Stock Solution

10 mg of Phenytoin was accurately weighed into 10 ml volumetric flask and dissolved in small quantity of 6.8 pH Phosphate Buffer. The volume was made up to 10 ml with the 6.8 pH Phosphate Buffer to get a concentration of (1000 µg/ml) SS-I. From this, 1 ml was withdrawn and diluted to 10 ml with distilled water to get a concentration of (100 µg/ml) SS-II.

Calibration Curve in 6.8 pH Phosphate Buffer

From the standard stock solution (SS-II), 0.2, 0.4, 0.6, 0.8,1 and 1.2 ml were withdrawn and volume was made up to 10 ml with 6.4 phosphate buffer to give a concentration of 2, 4, 6,8 10 and 12µg/ml. Absorbance of these solutions was measured against a blank of 6.8 pH Phosphate Buffer at 202 nm for Phenytoin and the absorbance values was summarized. Calibration curve was plotted, drug concentrations versus absorbance was also given in the figure.

Drug Excipient Compatibility Studies by I.R Spectroscopy

Infra Red spectroscopy is one of the most powerful analytical techniques to identify functional groups of a drug. The pure drug and its formulation were subjected to IR studies. In the present study, the potassium bromide disc (pellet) method was employed.

Formulation of Orally Disintegration Tablets of Phenytoin[6-9]

The Phenytoin oral disintegrating tablets were prepared using super disintegrants by direct compression method. Phenytoin tablet each weighing 250 mg containing 100 mg of Phenytoin was formulated as follows,

All the ingredients were passed through #60mesh sieve separately. The drug & Mannitol were mixed by adding small portion of each at a time and blending it to get a uniform mixture and kept aside.

Then the other ingredients were mixed in geometrical order and passed through coarse sieve (#44 mesh) and the tablets were compressed using hydraulic press. Compression force of the machine was adjusted to obtain the hardness in the range of 3.5-5 kg/cm2 for all batches. The weight of the tablets was kept constant for all formulations F1 to F12 (250 mg).

Table 3: Formulation table for Phenytoin oral disintegrating tablet

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Phenytoin	100	100	100	100	100	100	100	100	100	100	100	**100**
Croscarmellose Sodium	6.25	12.50	18.75	25.00	--	--	--	--	--	--	--	**--**
Lycoat	--	--	--	--	6.25	12.50	18.75	25.00	--	--	--	**--**
Ludiflash	--	--	--	--	--	--	--	--	6.25	12.50	18.75	**25.00**
Mannitol	75.75	69.5	63.25	57	75.75	69.5	63.25	57	75.75	69.5	63.25	**57**
M.C.C	60	60	60	60	60	60	60	60	60	60	60	**60**
Aspartame	4	4	4	4	4	4	4	4	4	4	4	**4**
Magnesium stearate	2	2	2	2	2	2	2	2	2	2	2	**2**
Talc	2	2	2	2	2	2	2	2	2	2	2	**2**
Total weight(mg)	250	250	250	250	250	250	250	250	250	250	250	250

Evaluation Parameters (Pre compression Parameters[8-12]

Method Preparation of Mixed Blend of Drug and Excipients

All the materials were passed through sieve no. 80. Required quantity of each ingredient was taken for each specified formulation (Mentioned in Table 3) and all the ingredients were subjected to grinding to a required degree of fineness (except magnesium stearate and talc). The powdered blend was evaluated for the below flow properties :

- Angle of repose
- Bulk density
- Tapped density
- Compressibility index
- Hausner's Ratio

Evaluation of Tablets (Post compression parameters)[10-14]

The following tests for tablets were calculated:

- Weight variation test
- Tablet hardness
- Tablet friability
- In-Vitro Disintegration time
- Thickness and Diameter
- Drug content uniformity
- In vitro Dissolution Study

Data Analysis (Curve fitting analysis)

To analyse the mechanism of the drug release rate kinetics of the dosage form, the data obtained were plotted as:[15-17]

- Cumulative percentage drug released Vs time (Zero order plot)
- Log cumulative percentage drug remaining Vs Time (First order plots)

Zero order model

The pharmaceutical dosage forms following these profiles release the same amount of drug by unit of time and it is the ideal method of drug release in order to achieve a pharmacological prolonged action. The following relation can, in a simple way, express this model:

$$Qt = Q0 + K0t$$

Where,
Qt is the amount of drug dissolved in time t,
Q0 is the initial amount of drug in the solution and K0 is the zero order release constant.
To study the release kinetics, data obtained from in vitro drug release studies were plotted as cumulative amount of drug released versus time

First order model

The application of this model to drug dissolution studies was first proposed by Gibaldi and Feldman (1967) and later by Wagner (1969). This model has been also used to describe absorption and/or elimination of some drugs, although it is difficult to conceptualise this mechanism in a theoretical basis **.**

$$\log Qt = \log Q0 + (K1/2.303)$$

Where,
Qt is the amount of drug released in time t,
Q0 is the initial amount of drug in the solution and
K1 is the first order release constant.
The data obtained are plotted as log cumulative percentage of drug remaining vs. time which would yield a straight line with a slope of-K/2.303.

RESULTS

Solubility studies

Solubility of Phenytoin was carried out at 25^0C using 0.1N HCL, 6.8 phosphate buffer, 7.4pH buffer and purified water.

Table 4: Solubility Studies

MEDIUM	SOLUBILITY (µg/ml)
6.4 pH Phosphate buffer	0.513
6.8 pH Phosphate buffer	0.998
7.4 pH Phosphate buffer	0.685
0.1N HCl	0.450

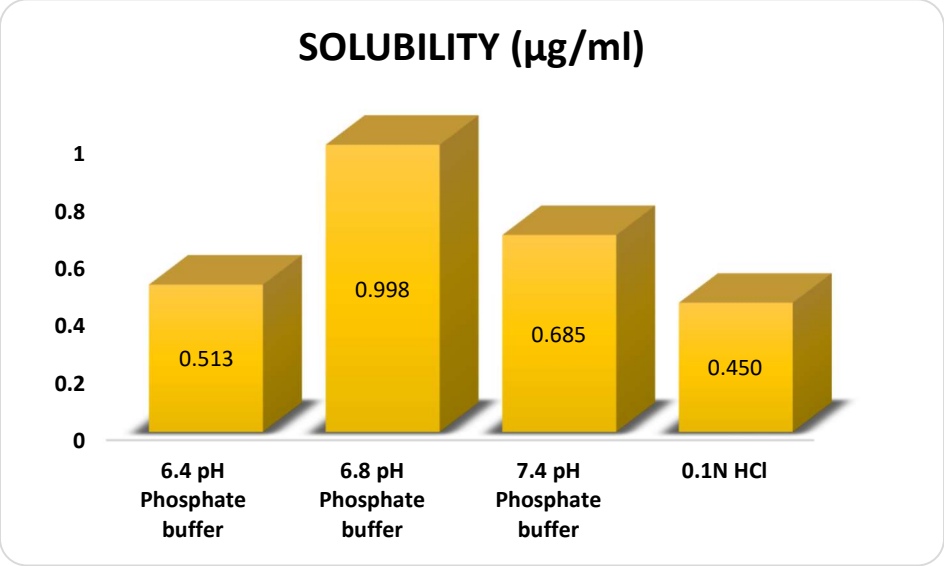

Fig 2: Graphs for the solubility studies of pure Drug

Discussion: From the above conducted solubility studies in various buffers, we can say 6.8 pH phosphate Buffer has more solubility when compared to other buffer solutions.

Determination of λ_{max}

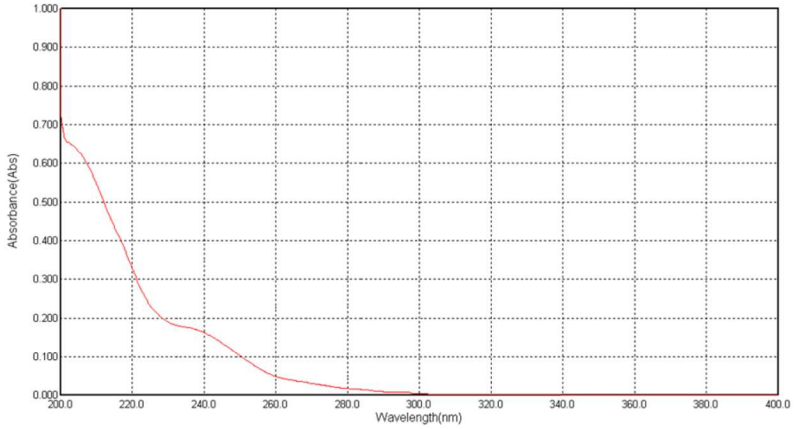

Fig 3: UV Spectrum curve of Phenytoin

The Absorption maxima of Phenytoin drug in the 100% concentration by using 6.8 pH Phosphate buffer was found to be at 202 nm by using Single Beam Spectrophotometer(YIS-294).

Calibration curve of Phenytoin in 6.8 pH phosphate Buffer

Table 5: Calibration curve of Phenytoin in pH 6.8 phosphate buffer

Concentration(µg/ml)	Absorbance
0	0
2	0.137
4	0.257
6	0.395
8	0.524
10	0.661
12	0.787

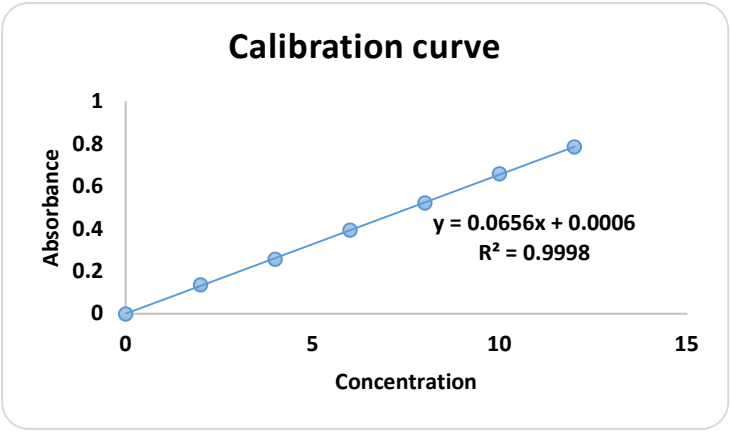

Fig 4: Standard graph of Phenytoin

The linearity was found to be in the range of 2-12µg/ml in pH 6.8 phosphate buffer. Regression analysis was selected because it minimizes the deviation and correct the variance heterogeneity. The regression line was defined by its slope (m) and its intercept (C) for normal regression analysis was found as 0.0656 and 0.0006, with regression coefficient of 0.9998 respectively. The regression value was closer to 1 indicating the method obeyed Beer-lamberts' law.

Drug excipient compatibility (FTIR Studies)

Drug and excipient compatibility was confirmed by comparing spectra of FT-IR analysis of pure drug with that of various excipients used in the formulation.

PURE DRUG

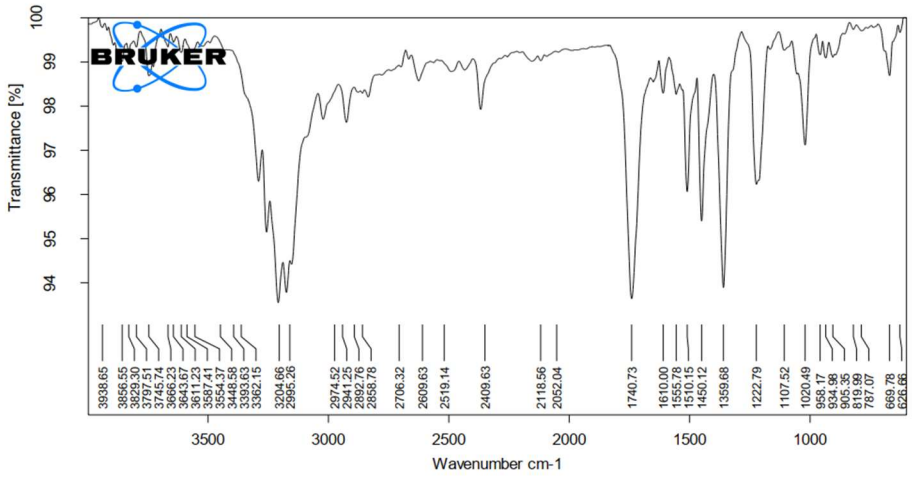

Fig 5: IR spectrum of Phenytoin

Optimized formulation

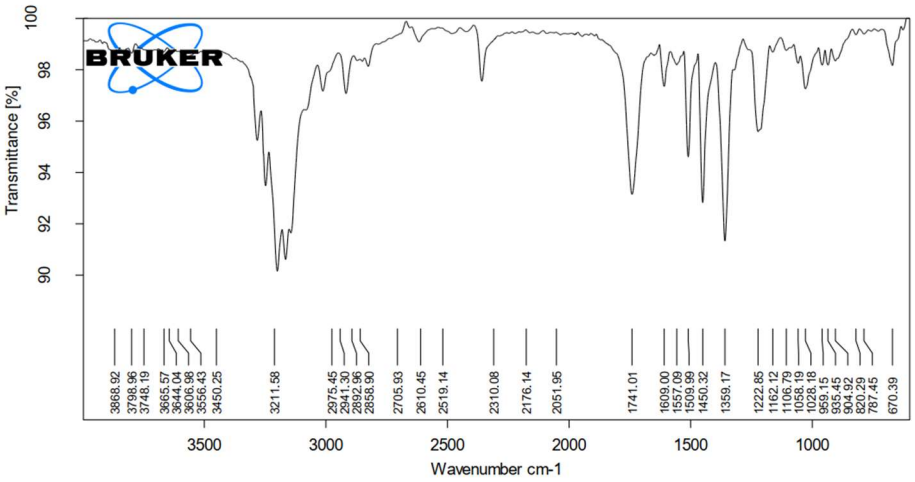

Fig 6: IR spectrum of Optimized formulation

The FTIR spectrum of pure Phenytoin, prepared Oral Disintegration Tablets of Phenytoin formulation by Direct Compression Techniques are shown in Figure 5 & 6 respectively. From the drug excipient compatibility studies we observe that there are no interactions between the pure drug (Phenytoin) and optimized formulation (Phenytoin + excipients) which indicates there are no physical changes.

Characterization of blend

Table 6: Pre-Compression parameters

Formulation Code	Derived properties		Flow properties		
	Bulk density (mean± SD)	Tapped density (mean± SD)	Angle of repose (mean± SD)	Carr's index (mean± SD)	Hausner's ratio (mean± SD)
F1	0.468±0.005	0.547±0.004	25.58±0.42	13.37±1.49	1.14±0.09
F2	0.484±0.006	0.556±0.006	26.87±0.28	13.69±1.54	1.13±0.04
F3	0.472±0.002	0.575±0.003	24.65±0.47	16.85±1.16	1.15±0.02
F4	0.496±0.007	0.589±0.004	27.66±0.26	13.46±1.16	1.16±0.04
F5	0.443±0.006	0.562±0.003	24.85±0.78	14.45±1.15	1.18±0.02
F6	0.465±0.007	0.584±0.004	26.58±0.22	16.87±1.21	1.14±0.05
F7	0.471±0.004	0.589±0.009	23.29±0.48	13.39±1.26	1.14±0.02
F8	0.489±0.006	0.595±0.006	28.45±0.35	13.45±1.42	1.13±0.09
F9	0.471±0.002	0.576±0.007	26.55±0.74	14.26±1.61	1.16±0.05
F10	0.496±0.003	0.587±0.003	25.66±0.28	12.47±1.26	1.15±0.06
F11	0.521±0.004	0.616±0.006	27.85±0.36	13.85±1.42	1.13±0.07
F12	0.539±0.002	0.634±0.005	28.97±0.35	11.25±1.24	1.11±0.02

The angle of repose of different formulations was ≤ 28.97±0.35 which indicates that material had good flow property. So, it was confirmed that the flow property of blends was free flowing. The bulk density of blend was found between 0.443±0.006 g/cm^3 to 0.539±0.002 g/cm^3. Tapped density was found between 0.547±0.004 g/cm^3 to 0.634±0.005 g/cm^3.These values indicate that the blends had good flow property. Carr's index for all the formulations was found to be between 11.25±1.24-16.87±1.21 and Hausner's ratio from 1.11±0.02 -1.18±0.02 which reveals that the blends have good flow character.

Characterization of tablets

Post Compression parameters

All the batches of tablet formulations were characterized for official evaluation parameters like Weight variation, Hardness, Friability, Tablet thickness and drug content and results are shown in the table.

Table 7: Characterization Phenytoin oral disintegrating tablets

Formulation	Average Weight (mg)	Thickness (mm)	Hardness (kp)	Friability (%)	Disintegrating time(sec)
F1	200.6±0.08	3.9±0.04	4.4±0.01	0.59±0.02	18.41±0.07
F2	201.1±0.12	3.7±0.03	4.0±0.03	0.57±0.06	16.25±0.08
F3	199.5±0.13	3.6±0.02	3.8±0.02	0.63±0.08	15.31±0.06
F4	201.2±0.12	3.5±0.03	4.3±0.01	0.69±0.02	13.48±0.07
F5	202.5±0.08	3.7±0.05	4.6±0.01	0.62±0.08	17.14±0.09
F6	202.3±0.11	3.9±0.09	4.4±0.06	0.67±0.06	15.25±0.07
F7	200.5±0.10	3.7±0.07	4.8±0.05	0.69±0.04	14.16±0.05
F8	201.4±0.07	3.8±0.05	4.7±0.07	0.49±0.08	13.24±0.02
F9	202.6±0.11	3.6±0.06	4.6±0.08	0.74±0.02	14.17±0.06
F10	199.9±0.08	3.9±0.07	4.7±0.06	0.45±0.05	12.16±0.02
F11	198.2±0.11	3.6±0.05	4.4±0.07	0.63±0.09	11.25±0.12
F12	200.1±0.05	4.1±0.05	4.8±0.06	0.45±0.07	9.47±0.15

Hardness of the tablet was acceptable and uniform from batch-to-batch variation, which was found to be 3.8±0.02– 4.8±0.06 kg/cm^2 and thickness was found to be 3.5±0.03-4.1±0.05 mm. All the formulations passed the weight variation test as the % weight variation was within the pharmacopoeial limits of the tablet weight. Friability values were found to be less than 1% in all the formulations F1 – F12 and considered to be satisfactory ensuring that all the formulations are mechanically stable. Disintegration time as per IP, for all the formulations was found to be between 18.41±0.07-9.47±0.15seconds, which was well within IP limit. Formulations with Ludiflash as super disintegrants shows quicker disintegration among all the formulations. Ludiflash with 1:0.5 ratio (Drug and Polymer) concentration as a super disintegrant shows very less disintegration time.

Drug content uniformity of formulations

The prepared formulations were analyzed for drug content and the data is reported in below Table. The drug content was found to be within the limits which show that the drug was uniformly distributed in all the formulations.

Table 8: Drug content uniformity of formulations F1-F12

Formulation	% of drug content
F1	94.18±1.18
F2	95.43±1.26
F3	97.26±1.45
F4	98.48±1.85
F5	96.56±1.29
F6	97.28±1.40
F7	98.45±1.35
F8	98.29±1.19
F9	97.46±1.45
F10	98.78±1.38
F11	98.36±1.45
F12	99.58±1.18

% Drug content values of formulation F1 – F12 was found to be in the range of 94.18±1.18-99.58±1.18%

Dissolution studies

The prepared tablets were subjected to dissolution studies in order to know the amount drug release. As the concentration of super disintegrant increased, the drug release time decreased.

Table 9: % Cumulative drug release of formulations F1-F6

Time (Min)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
5	25.45±1.45	32.28±1.54	43.18±1.32	50.42±1.51	28.28±1.20	37.17±1.67
10	48.75±1.64	49.15±1.95	60.17±1.02	62.26±1.45	52.15±1.62	55.42±1.54
20	63.86±1.84	60.48±1.67	69.31±1.65	79.18±1.36	65.47±1.27	67.16±1.20
30	79.38±1.57	76.26±1.57	79.46±1.25	86.25±1.20	81.15±1.54	76.25±1.65
45	85.21±1.78	83.18±1.29	90.82±1.20	92.41±1.74	88.87±1.56	89.41±1.84
60	94.44±1.62	96.48±1.58	97.12±1.36	98.58±1.62	95.48±1.28	96.84±1.26

Table 10: % Cumulative drug release of formulations F7-F12

Time (Min)	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	**0**
5	46.25±1.28	54.94±1.48	39.38±1.21	44.86±1.42	49.21±1.74	**58.84±1.25**
10	68.47±1.67	69.64±1.16	48.85±1.45	52.24±1.67	54.81±1.56	**67.67±1.25**

20	73.15±1.25	77.25±1.48	56.23±1.61	59.72±1.55	67.98±1.25	**78.41±1.16**
30	81.26±1.75	88.64±1.48	67.53±1.28	76.32±1.67	73.85±1.57	**89.25±1.19**
45	90.78±1.61	92.15±1.25	89.74±1.64	92.48±1.45	89.25±1.68	**95.45±1.26**
60	98.29±1.74	98.75±1.25	95.85±1.94	98.42±1.84	98.46±1.21	**99.85±1.46**

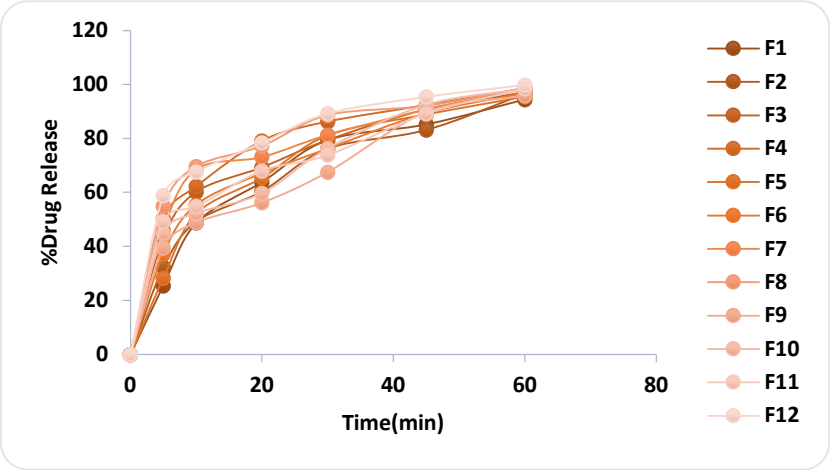

Fig 7: %DR of F1-F12

From the invitro drug release studies it was observed that the formulations containing Croscarmellose Sodium (F1-F4) as super disintegrant in the concentrations of (6.25mg, 12.50mg, 18.75mg and 25.00mg), the Formulation F1, F2, F3 shows 94.44±1.62%, 96.48±1.58, 97.12±1.36% drug release at the end of 60 minutes. Whereas F4 shows 98.58±1.62% drug release at the end of 60 minutes. Whereas the formulations containing Lycoat (F5-F8) as super disintegrant in the concentrations of 6.25mg, 12.50mg, 18.75mg and 25.00mg) shows 95.48±1.28%,96.84±1.26%, 98.29±1.74% and 98.75±1.25%, drug release at the end of 60minutes.While the formulations containing super disintegrant such as Ludiflash (F9-F12) in the concentrations of (6.25mg, 12.50mg, 18.75mg and 25.00mg) shows 95.85±1.94%, 98.42±1.84%, 98.46±1.21, 99.85±1.46% drug release at the end of 60 minutes. By comparing the dissolutions profiles of formulations F1-F12 containing super disintegrants in the concentrations of (6.25mg, 12.50mg, 18.75mg and 25.00mg), F12 containing 25mg Ludiflash shows 99.85±1.46% drug release at the end of 60min. So F12 formulation was considered as the optimized formulation. Further kinetics were measured for F12 formulation.

Table 11: Order of kinetic values of Formulation F12

Order of kinetics	Zero order	First order
Regression values	0.638	0.903

The drug release from the oral disintegrating tablets was explained by the using mathematical model equations such as zero order, first order methods. Based on the regression values it was concluded that the optimized formulation F12 follows First order drug release.

SUMMARY AND CONCLUSION

The present study is an attempt to select the best possible diluent - disintegrant combination to formulate Oral disintegrating tablets of Phenytoin, which disintegrates in matter of seconds in the oral cavity, thereby reducing the time of onset of pharmacological action. Lycoat, Croscarmellose sodium and Ludiflash, were used as disintegrants. In all the formulations, and Magnesium stearate and talc were used as lubricant and glidant respectively.

The results of the drug – excipient compatibility studies revealed that there was no chemical interaction between the pure drug and excipients. Direct Compression Technique was employed to formulate the tablets, because of its cost effectiveness and due to reduced number of manufacturing steps. The precompression parameters like bulk density, tapped density, Carr's index and angle of repose were determined. All the formulations showed acceptable flow properties. The post compression parameters like the hardness, thickness, friability and weight variation,

disintegration time, disintegration time in oral cavity and Invitro release were carried out and the values were found to be within IP limits. The percentage drug content of all the tablets was found to be between 94.18±1.18-99.58±1.18% of Phenytoin, which was within the acceptable limits. Among all the formulations F12 shows 99.85±1.46% drug release at the end of 60min. F12 contains Ludiflash (25mg), it shows better % drug release when compared to other formulations. So, F12 was considered as the optimized formulation. The drug release kinetics shows that the optimized formulation F12 follows First order drug release.

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