

FORMULATION DESIGN OF RAPIDLY DISINTEGRATING PHENOBARBITONE TABLETS BY DIRECT COMPRESSION METHOD**MAHADEVAPPA V. RAMPURE*., BASAWARAJ BENDEGUMBLE., S. APPALA RAJU., RAGHUNANDAN DESHPANDE AND P.V. SWAMY**

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ABSTRACT

In the present work, fast dissolving phenobarbitone tablets were prepared by direct compression method with a view to enhance patient compliance. The methodology worked out was by using three superdisintegrants (2-8%w/w) i.e., L-hydroxypropyl cellulose (L-HPC), pregelatinized starch, Crospovidone with varying concentration of microcrystalline cellulose(5-15%w/w) were used and directly compressible mannitol (Pearlitol SD 200) was used as a diluent to enhance the mouth feel. The prepared batches of tablets were evaluated for hardness, friability, drug content uniformity and *In-vitro* dispersion time (approximately 7 s). Three promising formulations were tested for drug release pattern (in pH 6.8 phosphate buffer), short term stability (at 40%75% RH for three months) and drug-exciipient interaction (IR spectroscopy). Among the promising formulations, the formulations FCP₃ (containing 8% w/w of crospovidone and 15% w/w of microcrystalline cellulose) emerged as the overall best formulation ($t_{50\%}$ 1.45 min) based on the in-vitro drug release compared to conventional commercial tablet ($t_{50\%}$ 15 min). Short-term stability studies on the formulations indicated that there are no significant changes in drug content and *In-vitro* dispersion time.

KEY WORDS

Rapidly disintegrating tablets, phenobarbitone, direct compression, crospovidone, microcrystalline cellulose. pre-gelatinized starch, L-hydroxypropyl cellulose

INTRODUCTION

Many patients find it difficult to swallow tablets and hard gelatin capsules and thus do not comply with prescription, which results in high incidence of non-compliance and ineffective therapy. It is estimated that 70% of the population is affected by this problem. Recent advances in novel drug delivery systems (NDDS) aim to enhance safety and efficacy of drug molecule by formulating a

convenient dosage form for administration and to achieve better patient compliance. One such approach is rapidly disintegrating tablets.¹⁻⁴ Phenobarbitone is a barbiturate that may be used as antiepileptic to control partial and generalized tonic-clonic seizures⁵. It has low aqueous solubility, poor dissolution and low bioavailability. This drug is widely used in pediatric patients for the control of seizures: hence, it was considered as a suitable drug

candidate for improving the patient compliance, by formulating rapidly disintegrating tablets.

MATERIALS AND METHODS

Phenobarbitone (AFD, Bangalore) was gift sample. Commercial phenobarbitone tablets (Gardinal 30) and crospovidone (CP), pregelatinized starch (PGS), LHPC-11, MCC 102 directly compressible mannitol (Pearlitol SD200), Sodium stearyl fumarate (SSF) and aspartame (Strides Arco Labs, Bangalore) were gift samples. All other chemicals used were of analytical reagent grade.

EXPERIMENTAL

Preparation of fast dissolving tablets of Phenobarbitone: Fast dissolving tablets of phenobarbitone were prepared by direct compression method⁶ according to the formulae given in Table 1. All the ingredients were passed through #60 mesh separately, weighed and mixed in geometrical order. Then lubricant and glidant (# 200 mesh) were added and mixed for further 5 min. The blend thus obtained was directly compressed using 8 mm flat round punches into tablets of 150 mg on a 10-station rotary tablet machine (Clit, Ahmedabad, India).

Table-1
Composition of different batches of fast dissolving tablets of Phenobarbitone

Ingredients (mg/tablet)	Formulation code												
	F ₀	FL ₁	FL ₂	FL ₃	FPG ₁	FPG ₂	FPG ₃	FCP ₁	FCP ₂	FCP ₃	C ₁	C ₂	C ₃
Phenobarbitone	30	30	30	30	30	30	30	30	30	30	30	30	30
L-HPC	-----	3	6	12	-----	-----	-----	-----	-----	-----	6	-----	----
PGS	-----	-----	-----	-----	3	6	12	-----	-----	-----	-----	12	----
Crospovidone	-----	-----	-----	-----	-----	-----	-----	3	6	12	-----	----	3
Avicel (PH 102)	15	7.5	15	22.5	7.5	15	22.5	7.5	15	22.5	-----	-----	-----
Aspartine	3	3	3	3	3	3	3	3	3	3	3	3	3
Flavour	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
S S F	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75
Talc	3	3	3	3	3	3	3	3	3	3	3	3	3
Mannitol (Pearlitol SD 200)	96.75	101.2 5	90.75	77.2 5	101.2 5	90.75	77.25	101.2 5	90.75	77.25	105.7 5	99.75	108.75

F₀ - Control Formulation, FL – LHPC, FPG – Pregelatinized Starch, FCP – Crospovidone, C₁ – Only LHPC, C₂ – Only Pregelatinized Starch and C₃ – Only Crospovidone.

Evaluation of tablets: For the weight variation twenty tablets were selected at random and assessed individually using an electronic balance (BL-220H, Shimadzu, Japan).. The individual weights were compared with the average weight for determination of weight variation⁷. Tablets were also evaluated for hardness (n=3) using a Monsanto hardness tester (Campbell, India), friability (n=10) using a Roche friability apparatus (Electrolab, India,) and thickness (n=3) using vernier calipers (Baker Gauges Ltd., India) respectively. For content uniformity test, ten tablets were weighed and powdered, a quantity of powder equivalent to 10 mg of phenobarbitone was extracted in methanol and liquid was filtered. The phenobarbitone content was determined by measuring the absorbance at 263.6 nm using a spectrophotometer (UV 1700 Pharmaspec, Shimadzu, Japan.) after appropriate dilution with

methanol. The drug content was determined using the standard calibration curve. The mean percent drug content was calculated as an average of three determinations⁸. For determination of In-vitro dispersion time, (n=3), one tablet, was placed in a beaker containing 10 ml of pH 6.8 phosphate buffer at 37±0.5° and the time required for complete dispersion was determined⁹. For determination of wetting time (n=3) and water absorption ratio (n=3) the method reported by Sunada et al¹⁰ was followed. The results are shown in Table 2. IR spectra of the pure drug and its formulation were obtained by KBr pellet method using Perkin-Elmer FTIR series 1615 (USA) spectrophotometer in order to rule-out drug-carrier interactions.

Table 2
Evaluation of fast dissolving tablets of phenobarbitone

Formulation	Hardness* (Kg/cm ²)± SD	Thickne ss* (mm)±S D	Friability (%)	Percent drug content*± SD	In vitro dispersion time* (s)±SD	Wetting time*(s)±SD	Water absorption ratio (%)
F ₀	2.90±0.15	2.33	0.75	98.25±1.12	169.66±2.4 9	171±1.90	50.00±2.78
FL ₁	2.80±0.10	2.21	0.62	95.68±0.59	70±1.63	71±1.62	52.2± 1.53
FL ₂	2.75±15	2.28	0.85	97.96±1.38	46.33±1.24	48±1.89	63.41 ±1.13
FL ₃	2.85±0.21	2.24	0.48	99.03±0.78	22.66±1.52	23±1.59	74.90± 1.20
FPG ₁	2.70±0.10	2.20	0.80	97.76±0.73	76.33±1.24	77±0.80	57.50±0.75
FPG ₂	2.83±0.15	2.25	0.50	99.46±0.71	56.66±0.94	57±1.06	62.93± 1.51
FPG ₃	2.76±0.01	2.31	0.41	99.42±1.02	26±2.16	28±2.87	64.95± 1.53
FCP ₁	2.50±0.10	2.23	0.52	101.27±0.74	16.33±2.05	17±0.84	70.37±1.00
FCP ₂	2.62±0.15	2.30	0.48	100.45±0.70	12.33±1.24	13±0.77	85.00±0.51
FCP ₃	2.51±0.102	2.22	0.68	100.50±0.84	7±0.81	9±0.25	85.92±0.26

C ₁	2.90±0.05	2.33	0.86	96.34±1.42	50.0±1.63	51±1.06	56.89±
C ₂	2.85±0.02	2.22	0.43	97.30±2.65	69.66±1.69	70±1.85	54.49±0.60
C ₃	2.90±0.10	2.28	0.80	99.25±0.54	51.16±1.11	53.25±1.90	58.20±1.78

In vitro drug release study: In- vitro dissolution of the formulated rapidly disintegrating tablets of phenobarbitone and one commercial conventional tablet was studied USP XXIII type-II¹¹ dissolution apparatus (TDT 06N, Electrolab, India.) employing a paddle stirrer at 50 rpm using 900 ml of pH 6.8 phosphate buffer at 37±0.5° as dissolution medium¹². One tablet was used in each test (n=3) and studies were run in triplicate.. Aliquots of dissolution medium (5 ml) were withdrawn at specific intervals of time and analyzed for drug content by measuring the absorbance at 263.6 nm. The volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium. Cumulative percent drug released was calculated and plotted against time.

Stability testing: Short-term stability studies on the optimized promising formulation (F₃) were carried out by storing the tablets (in amber colored rubber stoppered vials) at 40°/ 75% RH for 3 months¹³. At intervals of 1 month, the tablets were visually examined for any physical changes, changes in drug content and In-vitro dispersion time.

RESULTS AND DISCUSSION

Rapidly disintegrating tablets of phenobarbitone were prepared by direct compression method using L-hydroxypropyl cellulose (L-HPC), pregelatinized starch, Crospovidone along with varying concentration of microcrystalline cellulose were used and directly compressible mannitol (Pearlitol SD 200) was used as a diluent to enhance the mouth feel. A total of twelve formulations and a control formulation (F₀, without super-disintegrant) were designedAs the

material was free flowing (angle of repose value <30° and Carr's index <15) tablets obtained were of uniform weight (due to uniform die fill), with acceptable variation as per IP specifications i.e., below 7.5%. Drug content was found to be in the range of 95-101 %, which is within acceptable limits. Hardness of the tablets was found to be about 3.0 Kg/cm². Friability below 1% was an indication of good mechanical resistance of the tablets (Table 2). Based on the *in-vitro* dispersion time (7s), three promising formulations viz., FCP₃, FL₃ and FPG₃ were tested for *in vitro* drug release pattern (in pH 6.8 phosphate buffer), short term stability (at 40°/75% RH for 3 months) and drug interaction (IR spectroscopy). Among the promising formulations, the formulation FCP₃ (containing 8% w/w of crospovidone and mixture of 15% w/w of microcrystalline cellulose) emerged as the overall best formulation found to be promising and displayed *In-vitro* dispersion time of approximately 7 s.

In vitro dissolution studies on the promising formulations (FCP₃ FL₃, FPG₃), the control (C₀), were carried out in pH 6.8 phosphate buffer and the various dissolution parameter values, viz., percent drug dissolved in 5 minutes (D₅), percent drug dissolved 10 minutes (D₁₀)¹⁴, t_{50%}, t_{70%} and t_{90%} were calculated and the results are shown in Table 3. Among the promising formulations, FCP₃ has shown faster drug release (t_{50%} 1.45 min) compared to control formulations (t_{50%} 15 min.) when t_{50%} values were considered in pH 6.8 phosphate buffer and thus emerged as the overall best formulation.

Table 3
***In-vitro* dissolution parameters in pH 6.8 phosphate buffer.**

Formulation	D ₅ (%)	D ₁₀ (%)	t _{50%} (min)	t _{70%} (min)	t _{90%} (min)
CF	11.56	11.94	> 15	> 15	> 15
FCP ₃	90.10	96.37	1.45	3.13	5.92
FL ₃	72.25	90.11	1.78	5.29	9.98
FPGS ₃	68.69	89.35	1.85	5.79	> 15

FCP₃, FL₃ and FPGS₃ are rapidly disintegrating oral tablet formulations, CF is conventional commercial tablet formulation, D₅ is percent drug released in 5 min, D₁₀ is percent drug released in 10 min, t_{50%} is time for 50% drug release, t_{70%} is time for 70% drug release and t_{90%} is time for 90% drug release.

IR spectra of phenobarbitone and its promising formulation FCP₃ are shown in Figure 4. All the peaks of these spectra show similar frequencies. The peak at 717 cm⁻¹ is attributed to the out of plane deformation peak of C-H aromatic ring. The peak at 817 cm⁻¹ is due to the C-H bonding of the aromatic ring. The peaks at 1600 and 1706 cm⁻¹ are due to absorption of -C=O and C=C with six member rings. The peaks at 1310 and 1199 cm⁻¹ are due to C-H stretching and that 877 cm⁻¹ is due to out of plane N-H wagging. The peaks at

2938 and 3292 cm⁻¹ correspond to N-H and C-H stretching frequencies respectively. All these peaks are slightly shifted in the formulation. With overall analysis, we infer that there are no drug-excipient interactions in the phenobarbitone formulation. IR spectroscopic studies indicated that the drug is compatible with all the excipients. The IR spectrum of FCP₃ showed all the characteristic peaks of phenobarbitone, thus confirming that no interaction of drug occurred with the components of the formulation. Short-term stability studies of the above formulation indicated that there are no significant changes in drug content and *in vitro* dispersion time at the end of 3 months.

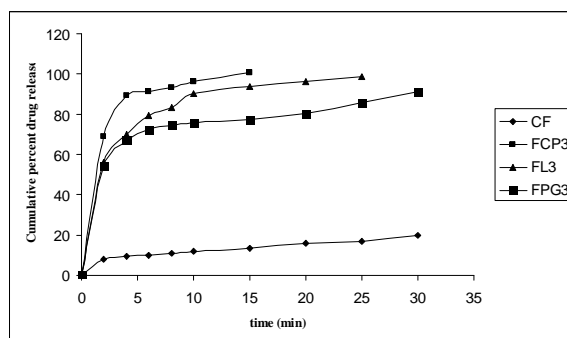


Fig.1.

In-vitro cumulative percent drug release versus time profile of formulations (FCP₃), (FL₃), in pH 6.8 phosphate buffer (n=3).

Plot showing percent cumulative drug release in pH 6.8 phosphate buffer from commercial tablet formulation CF (—◆—); rapidly disintegrating tablet FCP₃ (—■—); rapidly disintegrating tablet FL₃ (—▲—); rapidly disintegrating tablet FPG₃ (—●—).

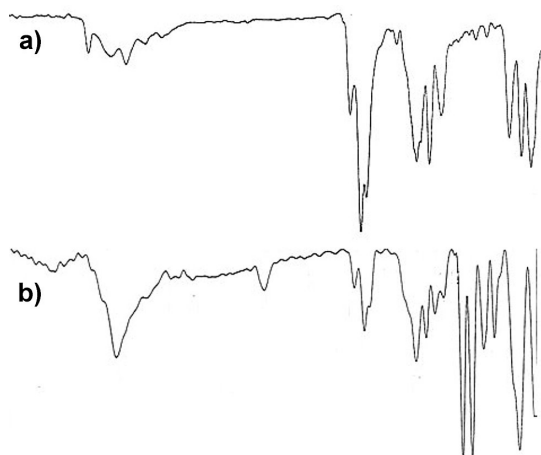


Fig 2

a) IR spectra of. a- pure drug, b) Ir psectra of promising formulation FCP₃

CONCLUSION

Superdisintegrant consisting of crospovidone with microcrystalline cellulose exhibit good flow and compression characteristics and exhibited quick disintegration and improved drug dissolution. Results revealed that it is possible to enhance the dissolution rate and bioavailability by direct compression technique using different superdisintegrants. The overall

results indicate that formulation FCP₃, which contains 8% w/w crospovidone, was better and satisfies all criteria as a rapidly disintegrating tablet.

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