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Research Article

PREPARATION AND EVALUATION OF PHENOBARBITAL ORODISPERSIBLE TABLETS

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ABSTRACT

Phenobarbital is an antiepileptic drug used in the treatment of epilepsy. Fast dissolving phenobarbitone tablets were prepared using direct compression to enhance patient compliance. The methodology technique depends on using three different superdisintegrants with different concentrations (5-15%w/w) i.e., sodium starch glycolate, croscarmelose, crospovidone, with varying concentrations of microcrystalline cellulose (10-25%w/w) to improve flowability. Directly compressible mannitol used as a diluent to enhance mouth feel and compressibility. The prepared formulas were evaluated for hardness, friability, disintegration time, and content uniformity. Crospovidone 10% with microcrystalline cellulose (25%) gave the acceptable friability (0.53±0.25%) and least disintegration time (12.07±0.23sec) and best flow property. Depending on the *in-vitro* and *in-vivo* disintegration time, the promising formulations were studied further for drug release pattern. Short term stability study (at 40º C/ 75% RH for 3 months), and light effect at room temperature study for the best formula.

Keywords: Orodispersible, Phenobarbital, Superdisintegrant.

INTRODUCTION

Orally disintegrating tablets (ODTs) is uncoated tablets intended to be placed in the mouth where they disintegrate within 3 min and disperse rapidly before being swallowed. [1]

The benefits of ODTs is to improve patients compliance, rapid onset of action, good stability and increased bioavailability which make these tablets popular as a dosage form of choice in the current market [2].

Orodispersible tablets are preferred for people suffering from dysphagia, institutional psychiatric patients as well as hospitalized patients suffering from a variety of disorders such as stroke, thyroid disorder, Parkinson's disease and other neurological disorders like multiple sclerosis, and cerebral palsy [1].

The basic approach in development of FDT is the use of superdisintegrants like cross linked carboxymethyl cellulose (croscarmellose), sodium starch glycolate (primogel), poly vinyl pyrollidone (poly plasdone) etc, which provide instantaneous disintegration of tablet after putting on tongue, their by release the drug in saliva [3].

MATERIALS AND METHODS

Materials

Phenobarbital, barbital® tablet, sodium starch glycolate, microcrystalline cellulose (avecil ph 102), talc, aspartame, and croscarmelose (Samara Drug Industry, Iraq), crospovidone (pharmaceutical Wuhan international Co. Ltd, China), mannitol, and magnesium stearate, (Riedel-De-Haen AG Seelze, Germany).

Method

Preparation of Phenobarbital Tablets

Each formula was formulated by mixing all the ingredients (except the lubricant) for 15 minutes after which the lubricant was added and blended for another 1 minute. The final mixture was compressed using a 9.6-mm single- punch tablet machine to get tablets of 200 mg weight.

Before tablets preparation, the mixture blends of all the formulation were subjected for pre compression parameter like bulk density, tapped density, angle of Repose, percentage compressibility and Hausner's ratio [4].

Table 1: Composition of the Phenobarbital orodispersible formulas

Contents / Formula no.	Phenobarbital (mg)	CP (mg)	CCS (mg)	SSG (mg)	Avicel 102 (mg)	Aspartame (mg)	Talc (mg)	Mg stearate(mg)	Mannitol Q.S. to
F1	15	10				4	4	2	200 mg
F2	15	20				4	4	2	200 mg
F3	15	30				4	4	2	200 mg
F4	15		10			4	4	2	200 mg
F5	15		20			4	4	2	200 mg
F6	15		30			4	4	2	200 mg
F7	15			10		4	4	2	200 mg
F8	15			20		4	4	2	200 mg
F9	15			30		4	4	2	200 mg
F10	15	20			20	4	4	2	200 mg
F11	15	20			30	4	4	2	200 mg
F12	15	20			40	4	4	2	200 mg
F13	15	20			50	4	4	2	200 mg

Evaluation of tablets

Micromeritic Properties (pre compression)

Angle of Repose (q)

Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and horizontal plane. The frictional force in a loose powder or granules can be measured by angle of repose.

$\tan q = h / r$

$q = \tan^{-1} (h/r)$

Where,

q is the angle of repose

h is height of pile

r is radius of the base of pile

The angle of repose is determined by fixed funnel method. The powder mass is allowed to flow through the funnel kept on a stand at a fixed height. The powders are carefully poured through the funnel on the Petri dish until the apex of conical pile just reached the tip of the funnel. The height of the pile and radius of the conical pile is noted and the angle of repose is calculated by the above equation [5].

Bulk Density and taped density

Bulk density is defined as the mass of a powder divided by the bulk volume. The bulk density of a powder depends primarily on particle size distribution, particle shape, and the tendency of the particles to adhere to one another [6].

LBD = Weight of the powder /Volume of the packing

TBD = Weight of the powder /Tapped volume of packing

Carr's Compressibility Index:

The compressibility index of the granules was determined by Carr's compressibility index [6].

Carr's Index (%) = (TBD – LBD)/ TBD x 100

Hausner's Ratio

Hausner's ratio is an indirect index of ease of powder flow**.** If the Hausner's ratio of the powder is near to 1.25 indicates better powder flow. It is calculated by the following formula [5]:

Hausner's ratio=tapped density/bulk density

< 1.25-good flow.

> 1.25-poor flow.

These results of angle of Repose, Carr's index, and Hausner's ratio are shown in table2.

Table 2: Flow-compression character [7]

Type of Flow	Compressibility Index	Hausner's ratio	Angle of Repose (θ)
Excellent	1-10	1-1.1	25-30
Good	11-15	1.12-1.18	31-35
Fair	16-20	1.19-1.25	36-40
Passable	21-25	1.26-1.34	41-45
Poor	26-31	1.35-1.45	46-55
Very poor	32-37	1.46-1.59	56-65
Extremely poor	>38	>1.6	>66

Post-Compression Parameters

1-Hardness and Friability

The crushing strength of the tablets was measured using a Monsanto hardness tester while tablet friability was assessed with a Roche friability tester. Twenty pre-weighed tablets were rotated at 25 rpm for 4 min and then the tablets were dusted and reweighed.The weight loss (%) was calculated [8].

2-Wetting time and water absorption ratio

Wetting time is closely related to the inner structure of the tablets and to the hydrophilicity of the excipients. It is obvious that pores size becomes smaller and wetting time increases with an increase in compression force or a decrease in porosity. A piece of tissue paper folded double was placed in a Petri plate containing 6ml of water. The tablet was placed on the paper and the time for complete wetting of the tablet was measured in seconds [4,9].

Water absorption ratio = (Wa –Wb)/ Wb

Where,

Wb = weight of tablet before absorption of water

Wa = weight of tablet after absorption of water.

Weight variation

Twenty tablets were randomly selected from each batch and individually weighed. The average weight of these selected tablets was calculated [9].

In-vitro disintegration time:

The disintegration time for all formulations was carried out using USP disintegration apparatus. Six tablets were placed individually in each tube of disintegration test apparatus and discs were placed. The phosphate buffer pH 6.8 was maintained at a temperature of 37°±2°C and time taken for the entire tablet to disintegrate completely was noted [10,11].

In-vivo disintegration time

The time required for complete disintegration in the oral cavity was collected from five healthy volunteers. All volunteers were told about the purpose of the test. Before the test, the mouth cavity was rinsed with a cup of water. The tablet was placed on the tongue and subsequently the tongue was gently moved. The time required for the elimination of any residue or fragment of the tablet was measured with a stopwatch and recorded as a disintegration time [12].

Drug content

Weigh and powder 20 tablets. An amount of the powder equivalent to 10mg of phenobarbitone was dissolved in 100ml of pH 6.8 buffer, filtered, and analyzed for drug content at 256nm using UV-Visible spectrophotometer (Carry win UV, Varian, Australia).

In-vitro drug release study

In-vitro dissolution of the designed phenobarbitone orodispersible and the commercial conventional tablets (Samarra's barbital® tablet) are studied using USP XXIII type-II dissolution apparatus (Copley dissolution 8000, Copley Scientific, U.K.) using a paddle stirrer at 50 rpm. The prepared phosphate buffer (250 ml) is added and the temperature at 37±0.5ºC as dissolution medium. For every test one tablet is used and the studies are run in triplicate (n=3). Aliquot of sample (5 mL) is taken periodically and evaluated for drug-content measurement at 256 nm absorbance. The volume of sample withdrawn at each time interval is replaced immediately with equal amount of newer dissolution medium and the cumulative percent of drug released is calculated. This release pattern and then plotted against time [13,14].

Stability Study

The Fast dissolving tablets of Phenobarbital of the best selected formula were placed in stability chamber at the temperature of 45°C and 75% RH. The tablets were taken after 3 months and evaluated for hardness, disintegration time and drug content [15].

RESULTS AND DISCISSION

Evaluation of the prepared Phenobarbital orodispersible tablets

The weight variation within the pharmacopeia limits of ±7.5% of the average weight and content uniformity tests of the prepared Phenobarbital orodispersible tablets complied with USP specification.

Effect of superdisintegrant type and concentration

Formulas F1-F9 were prepared to study the effect of type and concentration of super disintegrants; croscarmellose sodium,

sodium starch glycolate, and crospovidone, on in vivo and in-vitro disintegration time of the prepared Phenobarbital orodispersible tablet. The results shown in (table 5) indicate that crospovidone has the shortest in vivo DT(18.56-22.35 seconds) and in-vitro DT (17.7-20.22 seconds) followed by sodium starch glycolate, in-vivo DT (23.63-30.7 seconds) and in-vitro DT (21.75-28.95 seconds) then croscarmelose sodium, in-vivo DT (30.15-35.45 seconds) and in-vitro DT (27.27-33.59 seconds), the tablet that contain CP have shortest wetting time (9.46-13.2 seconds) which may attributed to strong wicking among the other super disintegrants. This result is in agreement with the result obtained by Goyani Sandip *et al*. [16]·Formula (F2) which contains 10% CP considered being the best concentration of superdisintegrant for fast disintegration.

Disintegration time for CP is faster than that of both SSG and CCS as mentioned and this may be due to the tendency of both SSG and CCS to swell with gel formation which make a viscous layer on the surface of the tablet and prevent water penetration to the tablet and delay swelling. While CP has no tendency to form a gel layer, so it's swelling and wicking will be faster [17].

Flow-compression characters of these formulas gave good compression parameters, Carr's index (10.01-13.88) and Hausner's ratio below 1.25 which considered being in the acceptable range according to Althaf *et al.* [18] While angle of Repose range is (36-37) which indicate that the powder mixture has fair flow character as shown in table (3).

Effect of Microcrystalline Cellulose (Avecil PH102) Concentrations

Formulas (F10-F13) prepared to improve flowability of powder mixture. Avicel PH 102 at 25% was the best concentration which give angle of Repose (23±0.834), Carr's index (14.5±0.265), and Hausner's ratio (1.170±0.07); so, the flow ability improved with good compressibility character, this due to the granular nature of avicel PH 102. It also was included in the formulation as a disintegrant where disintegration time (in-vitro and in-vivo) reduced when increasing its concentration, as shown in table (5) [19,20].

Physical Parameters

The hardness of all the prepared orodispersible tablets was kept constant at (3.5-4 kg/cm^2), which is satisfactory range for orodispersible tablet to study the effect of other factors in constant hardness [21].

The friability of all formulas of Phenobarbital orodispersible tablets was less than 1% which is acceptable according to BP criteria.

The content uniformity of the prepared Phenobarbital orodispersible tablet was complied with BP criteria. No tablet from ten tablets lies out of the range of 85-115% of the label claim. These results indicated that the dosage form had uniform distribution and proper dose of the active ingredient.

In-vitro drug release study

For dissolution study choosing the most appropriate and least disintegration time formulas (F2 and F13), also this study applied on the conventional tablet (Barbital®tablet) for comparison in release of plane and orodispersible tablets.

Figure (1) indicates that the prepared Phenobarbital orodispersible tablet F13 showed faster release rate than Barbital® tablets. The release time (T 75%) of the prepared Phenobarbital orodispersible tablet 4-fold faster than that of Barbital® tablet.

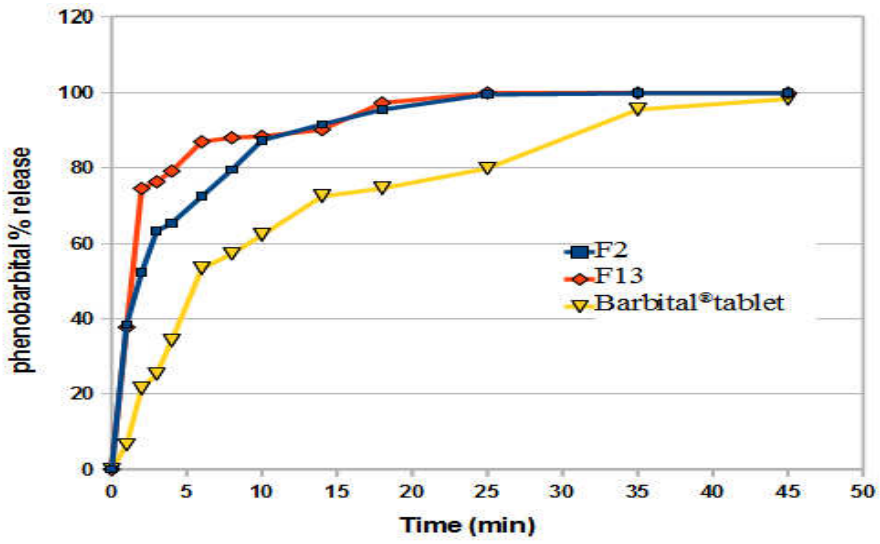

Fig. 1: Results of *in vitro* Drug Release Profile of F2, F13, and conventional tablet

Table 3: Flow-compression characters of prepared Phenobarbital orodispersible formulas powder (pre compression parameters)

Formula no.	Angle of Repose	Carr's Index	Hausner's ratio	Flow-compression character
1	36±1.2	11.84±0.621	1.130±0.03	Good to fair
2	37±0.74	11.46±0.256	1.129±0.03	Good to fair
3	37±1.32	11.42±0.872	1.128±0.02	Good to fair
4	36±0.56	10.82±0.512	1.121±0.04	Good to fair
5	37±1.75	11.3±0.827	1.127±0.02	Good to fair
6	37±1.23	10.01±0.132	1.111±0.03	Good to fair
7	36±0.976	13.32±0.915	1.153±0.02	Good to fair
8	36±0.34	13.73±0.435	1.159±0.04	Good to fair
9	37±1.05	13.88±0.231	1.161±0.02	Good to fair
10	28±0.74	11.89±0.383	1.134±0.02	Good
11	26±0.876	12.15±0.785	1.138±0.02	Good
12	25±1.43	13.23±0.966	1.150±0.03	Excellent to good
13	23±0.834	14.5±0.265	1.170±0.07	Excellent to good

Table 4: Evaluation of Orodispersible Tablets

Formula no.	Thickness (mm)	Hardness (kg/cm2)	Friability (%)	Weight variation
1	2.33±0.1	3.8±0.2	0.43±0.24	199.26±2.9
2	2.25±0.08	3.7±0.35	0.52±0.13	199.6±1.87
3	2.350.09	3.75±0.38	0.65±0.23	199.4±2.76
4	2.21±0.11	3.8±0.5	0.47±0.15	198.3±2.2
5	2.4±0.06	3.84±0.23	0.33±0.09	200.8±1.7
6	2.35±0.1	3.7±0.11	0.69±0.12	199.8±1.9
7	2.3±0.12	3.6±0.15	0.52±0.11	199.9±1.06
8	2.31±0.09	3.5±0.2	0.61±0.13	200.1±1.05
9	2.28±0.13	3.5±0.11	0.58±0.12	200.9±1.4
10	2.3±0.08	3.85±0.12	0.43±0.21	199.8±1.16
11	2.33±0.05	3.8±0.15	0.73±0.08	200.5±1.7
12	2.23±0.11	3.75±0.13	0.62±0.14	200.06±1.6
13	2.34±0.1	3.8±0.12	0.53±0.25	200.16±2.21

Table 5: Physical properties of orodispersible tablets

Formula no.	Disintegration time (sec)		Wetting time (sec)	Drug content uniformity %
	In vivo	In vitro		
1	22.35±1.12	20.22±0.65	13.2±0.65	96.2±0.38
2	18.56±1.07	17.7±0.98	9.46±0.24	96.3±1.74
3	20.67±2.32	19.2±1.05	10.35±0.37	97.4±0.26
4	35.45±3.65	33.59±2.14	48.3±1.53	96.8±0.61
5	33.31±3.13	31.72±3.17	39.45±2.75	98.2±1.72
6	30.15±2.63	27.27±1.43	36.8±2.11	99.8±0.34
7	26.72±3.45	25.58±1.84	47.58±3.84	101.2±0.24
8	23.63±2.22	21.75±1.56	39.12±4.66	97.2±0.74
9	30.7±1.18	28.95±1.94	43.46±2.95	101.5±0.31
10	16.83±1.61	14.46±0.94	10.89±1.04	99.5±0.46
11	14.52±2.83	13.67±0.58	10.26±0.86	99.7±0.42
12	14.14±1.43	13.36±1.05	8.93±0.36	101.1±0.15
13	13.43±1.16	12.07±0.23	7.35±0.19	98.9±0.25

Stability study

In term of overall parameters, formula F13 was considered as the selected best formula, thus it was subjected to stability study, the short term stability study show no changes in tablet hardness, friability, drug content, in vivo DT and dissolution rate at the end of the stability study period.

CONCLUSION

Overall, the results suggest that suitably formulated orodispersible tablets of phenobarbital containing 10% CP as a super disintegrant and 25% micro crystalline cellulose used to improve flowability of powder mixture and as disintegrant by direct compression method. The optimum selected formula (F13) has satisfactory physical resistance, fast in vivo disintegration time, high dissolution rate and good stability.

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