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FORMULATION, DEVELOPMENT AND EVALUATION OF CLOBAZAM ORODISPERSIBLE TABLETS USING NATURAL POLYMERS

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ABSTRACT

Epilepsy affects over 50 million people worldwide, 90% of whom are from developing nations. Design of new dosage forms has taken on a lot of significance as a means of enhancing compliance and making administration more convenient. The purpose of this effort is to build an orodispersible clobazam tablet which will begin working within a few minutes. The formulation evaluation of tablet was done according to standard methods. Results of pre compression parameters showed that the loose bulk density was found to be ranged from 0.325 gm/ml to 0.348 gm/ml while the tapped density ranged from 0.435 gm/ml to 0.456 gm/ml. The carr's index varied from 22.838 to 25.885. The Hausner's Ratio spanned from 1.296 to 1.349. The angle of repose found to be in range between 43^0 to 45^0. Hardness ranged within 3.1 to 3.4 kg/cm^2 while the friability varied from 0.568 to 0.745. The weight variation extends from 98 to 105. The thickness of tablet ranged from 1.36 to 1.63 while the % drug content seen to in between 97.74 to 98.85%. Beyond that the least disintegration time was observed for formulation F7 which is 36±3 seconds. The in vitro drug release data suggested that in just 15 minutes about 98.85% drug is released. From the obtained R^2 value it is clear that drug relase by formulation F7 follows zero order kinetics. From the results it is clear that it is clear that the drug-loaded oral dispersible tablet was reliable and exhibits an improved drug release profile.

Keywords: Epilepsy, Clobazam, Orodispersible tablet, Disintegration, Drug release

INTRODUCTION

One of the most prevalent major neurologic disorders, epilepsy affects up to 1% of the population, placing it second only to stroke in terms of prevalence. Epilepsy affects over 50 million people worldwide, 90% of whom are from developing nations. Although unexpected frequency seizures are a hallmark of epilepsy, epilepsy is a widespread neurological condition that affects people of all ages. Epilepsy does, in fact, have a bimodal onset that most frequently affects elderly adults and children. It is also a spectrum of disorders with varied degrees of severity, a large range of seizure types and causes, and a variety of effects on the affected person and their family. The difficulties that millions of people with epilepsy face include gaining access to high-quality healthcare, learning about and coordinating healthcare, medication, vocational, independent living, and other community services, as well as overcoming stigma and widespread public misconceptions. These difficulties go beyond actually living with epilepsy, its seizures, and coexisting health conditions. As a result, epilepsy places a tremendous strain on

affected people, their families, and society as a whole (Banerjee *et al*., 2009; Ellis *et al*., 2000; Benbadis, 2009).

Design of new dosage forms has taken on a lot of significance as a means of enhancing compliance and making administration more convenient. Conventional oral drug delivery presents a drug with a quick and complete release that may go as such without generating the desired effect. This could be because of the presence of food, the stomach's pH, enzymatic degradation, changes in GIT motility, and other factors, which would provide the drug insufficient time to be absorbed. Designing drug administration systems with organoleptic elegance and maximal patient acceptability in pediatrics and geriatrics has received a lot of attention recently (Bhutani *et al*., 2021; Sosnik *et al*., 2016).

Orodispersible tablets (ODTs) are also known as mouth-dissolving tablets, quick-dissolving tablets, fast-dissolving tablets, rapid-dissolving tablets, porous tablets, and rapidmelts. Despite all of the aforementioned terms, the USP has designated these dose forms as ODTs. Orodispersible tablets are those that quickly dissolve in the mouth before being swallowed, as defined by the European Pharmacopoeia. ODT is characterized by the US Food and Drug Administration as "A solid dosage form containing a medicinal substance or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon the tongue." ODTs typically disintegrate in a period of time between a few seconds and a minute (Nagar *et al*., 2011; Klancke, 2003).

The pharmacological class known as benzodiazepines includes clobazam. Clobazam increases GABAnergic transmission, notably chloride conductance in neurons, via acting on the GABAA receptor. Because of the resultant neuronal hyperpolarization, the action potential threshold rises and the frequency of neuronal firing decreases. Clobazam can be used to treat illnesses brought on by an excess of excitatory action potentials since it reduces the overall neuronal activity of the central nervous system. The purpose of this effort is to build an orodispersible clobazam tablet since it must begin working within a few minutes (Rupp *et al*., 1979; Gauthier and Mattson, 2015).

MATERIALS & METHODS

Reagent & Chemicals

Gellan Gum, Guar Gum, Gum Karaya, PVP K30, Talc, Magnesium stearate, Lactose, Mannitol was obtained from Loba chemie Pvt. Ltd. Mumbai.

Formulation development of orodispersible tablets of Clobazam using natural polymer

The orodispersible tablets of Clobazam were prepared using the Gellan Gum, Guar Gum and Gum Karaya as natural disintegrant, mannitol as diluent, aspartame as sweetening agent, alcoholic solution of polyvinyl pyrrolidone (PVP K-30) as binder and aerosil as flow promoter and magnesium stearate as lubricant.

Evaluation of Precompression Parameter

Angle of repose (θ): The frictional forces in a loose powder or granules can be measured by the angle of repose. This is the maximum angle possible between the surface of

a pile of powder or granules and the horizontal plane.

Bulk density: Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. Accurately weighed amount of granules taken in a 50 ml capacity measuring cylinder was tapped for 100 times on a plane hard wooden surface and estimated the LBD and TBD, calculated by using following formulas. Loose bulk density was calculated by dividing mass of powder by volume of packing while the tapped bulk density was estimated by dividing mass of powder by tapped volume of packing

Carr's index: Percent compressibility of powder mix was determined by Carr's compressibility index. The carrs index was calculated by substracting loose bulk density from tapped bulk density divided by tapped bulk density

Hausners ratio: It is determined by comparing tapped density to the bulk density by using Hausner's ratio value <1.25 shows better flow properties

Evaluation of post compression Parameter

Shape and colour of tablets

Uncoated tablets were examined under a lens for the shape of the tablet and colour was observed by keeping the tablets in light (Ravichandiran *et al*., 2009).

Thickness test

Three tablets were picked from each formulation randomly and thickness was measured individually (Ghosh and Pfister, 2005). It is expressed in mm and standard deviation was also calculated. The tablet thickness was measured using dial-caliper (Mitutoyo, Japan).

Weight variation test

Twenty tablets were selected randomly from each formulation and average weight was determined (Takagi *et al.*, 2005). The tablets were weighed individually and compared with average weight. The U.S Pharmacopoeia allows a little variation in the weight of a tablet. In all the formulations the tablets weight is more than 130 mg and less than 324 mg, hence 7.5% maximum difference allowed.

Hardness test

The hardness of tablet was measured by Pfizer hardness tester and results were expressed in Kg/cm^2 (Hirani *et al*., 2009).

Friability test

For this, 20 tablets were taken from each formulation and the friability was determined using Roche friabilator (Kuno *et al*., 2005). The equipment was run for 4min at 25 revolutions per minute. The tablets were taken out, dedusted and reweighted and % friability was calculated. The friability was determined by dividing loss in weight by dividing initial weight multiplied by 100. The test complies if tablets not loss more than 1% of their weight

Uniformity of drug content:

The test is mandatory for tablets with 10 mg or less weight of active ingredient. Ten randomly selected tablets from each formulation (F1 to F9) were finely powdered and Drug equivalent to 5mg of drug dissolved in 10 ml phosphate buffer (pH 6.8) sonicate it for 20 minutes, till the entire drug leached out from complex, then

the solution was filtered through whatman filter paper No. 41. From this Solution take 2 ml and Diluted up to 100 ml with phosphate buffer (pH 6.8) and the drug content was determined spectrophotometrically at 222nm (Tambe, 2018).

Dissolution rate studies

The prepared tablets were evaluated for *in vitro* drug release. The drug release studies were carried out using USP XXII paddle type Dissolution test apparatus. The dissolution study was carried out in 900 ml dissolution medium which was stirred at 75 rpm maintained at 37±0.2°C. The scheme of using the simulated fluids at different timing was as follows: A tablet placed in dissolution media (900 ml, phosphate buffer, pH 6.8) at 37±0.2°C. Samples were withdrawn at different time interval and compensated with same amount of fresh dissolution medium. Volume of sample withdrawn was made up to 10ml phosphate buffer (pH 6.8). The samples withdrawn were assayed spectrophotometrically at 222nm using UV visible spectrophotometer. The release of drug was calculated with the help of Standard curve of Clobazam.

RESULTS AND DISCUSSION

The loose bulk density was found to be ranged from 0.325 gm/ml to 0.348 gm/ml while the tapped density ranged from 0.435 gm/ml to 0.456 gm/ml. The carr's index varied from 22.838 to 25.885. The Hausner's Ratio spanned from 1.296 to 1.349. The angle of repose found to be in range between 43^0 to 45^0.

The post compression parameters was also evaluated. The hardness test was performed to know the tablet hardness. Hardness ranged within 3.1 to 3.4 kg/cm^2 while the friability varied from 0.568 to 0.745. The weight variation extends from 98 to 105. The thickness of tablet ranged from 1.36 to 1.63 while the % drug content seen to in between 97.74 to 98.85%. IP requirements indicate that the tablets' medication content must be between 95% and 105% of the declared amount. As a result, every ODT formulation complies with the IP standards.

Beyond that the least disintegration time was observed for formulation F7 which is 36±3 seconds. The in vitro drug release data suggested that in just 15 minutes about 98.85% drug is released. The same way that they are crucial for traditional tablets, in vitro dissolution studies are crucial for ODTs. Studies on the improved formulations' in vitro drug release were done at pH 6.8. The pH 6.8 was chosen to evaluate any pregastric absorption that might occur if some of the orodispersible formulation's particles got stuck in the denture and eventually would get absorbed through buccal mucosa. The release profile was clarified by the comparative examination of each formulation using in vitro kinetic parameters. When the mathematical model was applied it was seen that for zero & first order reaction the R^2 value was observed to be 0.976 & 0.807 respectively. From the obtained R^2 value it is clear that drug relase by formulation F7 follows zero order kinetics.

Table 1: Formulation of various batches using natural polymer

F. Ingredients (mg)	F1	F2	F3	F4	F5	F6	F6	F8	F9
API	5	5	5	5	5	5	5	5	5
Gellan Gum	10	15	20	-	-	-	-	-	-
Guar Gum	-	-	-	10	15	20			
Gum Karaya	-	-	-	-	-	-	10	15	20
PVP K30	10	10	10	10	10	10	10	10	10
Talc	10	10	10	10	10	10	10	10	10
Magnesium stearate	10	10	10	10	10	10	10	10	10
Lactose	40	35	30	40	35	30	40	35	30
Mannitol	15	15	15	15	15	15	15	15	15
Total wt.	100	100	100	100	100	100	100	100	100

Table 2: Results of pre-compression parameters of Clobazam

Formulation code	Parameters				
	Loose Bulk density(gm/ml)	**Tapped bulk density(gm/ml)**	**Carr's Index (%)**	**Hausner's Ratio**	**Angle of Repose**
F1	0.345	0.455	24.176	1.319	43^0
F2	0.335	0.452	25.885	1.349	43^0
F3	0.342	0.456	25.000	1.333	44^0
F4	0.325	0.435	25.287	1.338	43^0
F5	0.336	0.447	24.832	1.330	45^0
F6	0.348	0.454	23.348	1.305	44^0
F7	0.341	0.452	24.558	1.326	44^0
F8	0.348	0.451	22.838	1.296	43^0
F9	0.345	0.456	24.342	1.322	44^0

N=3 mean ±S.D

Table 3: Results of Post-Compression parameters of all formulations

F. Code	Hardness test (kg/cm^2)	Friability (%)	Weight variation (%)	Thickness (mm)	Drug content (%)
F1	3.1	0.568	102	1.45	98.78
F2	3.3	0.745	100	1.52	98.85
F3	3.2	0.669	98	1.47	98.65
F4	3.2	0.745	105	1.36	97.74
F5	3.3	0.632	103	1.54	98.65
F6	3.3	0.587	103	1.52	97.74
F7	3.4	0.745	99	1.63	99.65
F8	3.3	0.695	102	1.52	98.12
F9	3.4	0.771	100	1.47	97.85

Table 4: Results of *In vitro* disintegration time of all formulations

Formulation code	Disintegration Time (sec.)
F1	75±3
F2	65±2
F3	62±4
F4	55±6
F5	50±3
F6	52±4
F7	36±3
F8	42±2
F9	40±5

*N=3 mean±S.D

Table 5: *In-vitro* drug release data for optimized formulation F7

Time (min)	Square Root of Time(h)$^{1/2}$	Log Time	Cumulative*% Drug Release	Log Cumulative % Drug Release	Cumulative % Drug Remaining	Log Cumulative % Drug Remaining
1	1	0	52.23	1.718	47.77	1.679
5	2.236	0.699	69.98	1.845	30.02	1.477
10	3.162	1	78.85	1.897	21.15	1.325
15	3.873	1.176	98.85	1.995	1.15	0.061

N=6 mean±S.D

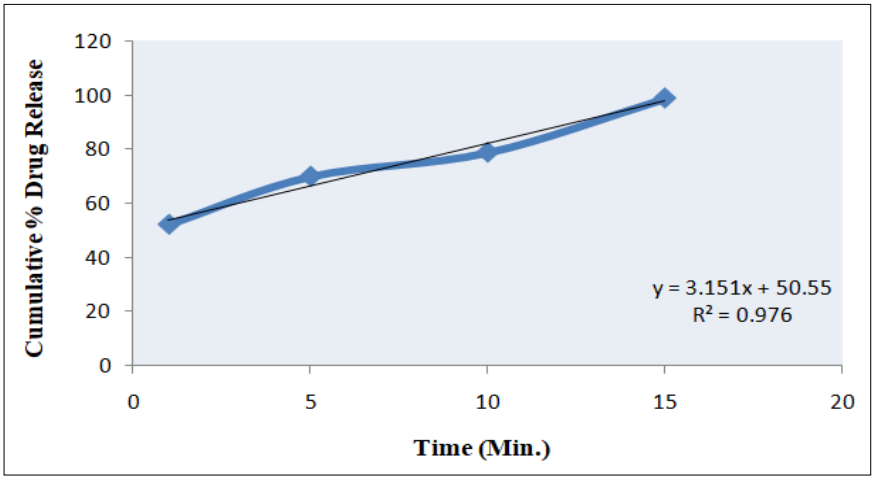

Figure 1: Graph of zero order release Kinetics of formulation F7

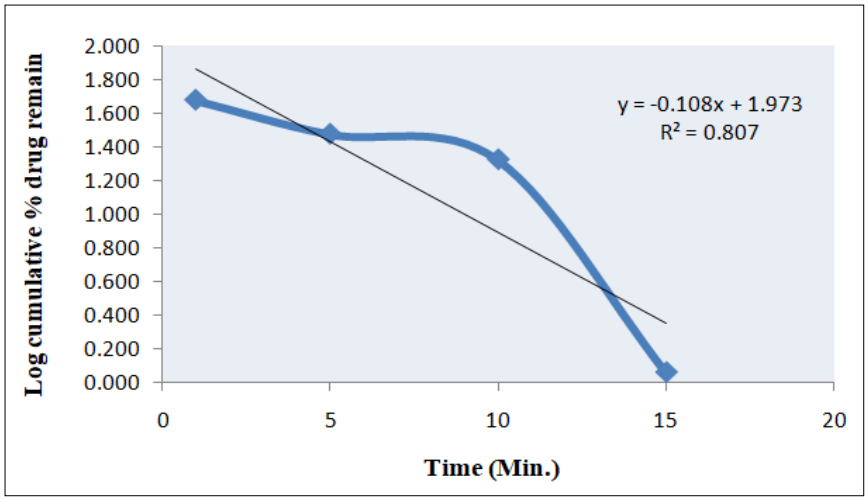

Figure 2: Graph of first order release kinetics of formulation F7

Table 6: Regression analysis data

Batch	Zero Order	First Order
	R^2	R^2
F7	0.976	0.807

CONCLUSION

The goal of the overall study was to formulate and evaluate the effectiveness of Clobazam orodispersible tablets using various superdisintegration agents. The results of the present study demonstrated that the tablets can be easily prepared using the direct compression technique without causing drug polymer incompatibility, resulting in faster release, increased bioavailability, and patient compliance with efficient therapy.

All of the formulas demonstrated acceptable release, but F7 was the one that was most chosen. According to the study, different ratios of Gellan Gum, Guar Gum & Gum Karaya can be employed for a better disintegration profile. A better release profile was seen with higher super disintegration agent concentrations. Consequently, it is clear that the drug-loaded oral dispersible tablet was reliable and exhibits an improved drug release profile.

DECLARATION OF INTEREST

The authors declare no conflicts of interests. The authors alone are responsible for the content and writing of this article.

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