Available online on 15.05.2025 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

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Research Article

Development and Evaluation of Baclofen Orodispersible Tablets by Sublimation Method

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Article Info:

Article History:

Received 11 Feb 2025
Reviewed 18 March 2025
Accepted 06 April 2025
Published 15 May 2025

Cite this article as:

Manjanna KM, Mounika C, Govind Reddy G, Siva Krishna G, Azharuddin M, Development and Evaluation of Baclofen Orodispersible Tablets by Sublimation Method, Journal of Drug Delivery and Therapeutics. 2025; 15(5):23-34
DOI:
http://dx.doi.org/10.22270/jddt.v15i5.7094

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Abstract

Purpose: Baclofen (BCF) is a novel muscle relaxant and antispasmodic drug that belongs to the BCS-III drug class, having low solubility and high permeability used for treating multiple sclerosis symptoms such as spasticity, stiffness, and pain. The aim of the present work is an attempt to develop orodispersible tablets of BCF by using camphor, menthol as sublimating agents and crospovidone, sodium starch glycolate as superdisintegrants.

Methods: The tablets were prepared by direct compression technique. The FTIR and DSC were used to investigate the drug excipients compatibility. The prepared tablets were subject to investigating thickness, hardness, weight variation, friability, drug content uniformity, swelling index, disintegration time and *In-vitro* drug release studies.

Results: The FTIR and DSC studies suggest that there is no interaction between the drug and excipients. All the pre-compressed parameters were shown in acceptable limits. The formulated batch (F6) tablets containing crospovidone (12%) and camphor (30%), showing rapid disintegration <18 sec and *In-vitro* drug release was achieving the highest release of 98.94%w/w at the end of 15 min, followed by Korsmeyer and Peppa's model, shows diffusion co-efficient n = 0.7606, which indicates the drug release from tablets by the non-Fickian diffusion mechanism.

Conclusion: The concentration of sublimating agent in the formulation creates highly porous tablets that significantly increase disintegration and promote faster drug release. Investigation of the research work was concluded that the addition of superdisintegrants and sublimating agents in the formulation of orodispersible tablets by direct compression is a novel technique to speed up drug release and improve patient compliance.

Keywords: Baclofen Orodispesiable Tablets, Sublimation Method, Crospovidone, Peppas model, Non- Fickain diffusion.

INTRODUCTION

Spasticity, a condition in which certain muscles are continuously contracted and associated with common neurological disorders like multiple sclerosis, stroke, cerebral palsy and spinal cord injury [1]. The patients suffering from these neurological disorders need certain novel medicinal products at the right time for immediate treatment administered either through the oral or peroral route [2]. Immediate treatment of therapy is possible through parenteral injection, as the drug directly enters the systemic circulation, providing rapid relief to patients. However, several challenges are associated with injections, including the need for a skilled professional for administration and the potential for pain at the injection site. Considering various drug delivery routes, orally administered dosage forms such as tablets and capsules are preferred due to their safety, accurate dosing, cost-effectiveness, ease of self-administration, and improved patient compliance [3]. The most popular solid oral dosage products such as powders, pills, tablets, capsules are administered for various diseases conditions [4]. These conventional immediate-release formulations provide clinically effective therapy by maintaining a steady-state concentration of the drug in plasma, ensuring the release of a satisfactory amount of the drug needed by the patient. Difficulty in swallowing solid dosage forms with water poses a challenge for all target patient groups, especially geriatrics, pediatrics, nomadic patients, and institutionalized psychiatric patients, as well as hospitalized or bedridden individuals suffering from various ailments such as stroke, thyroid disorders, and neurological conditions like multiple sclerosis and cerebral palsy [5]. A novel fast releasing oral drug delivery system has been developed to overcome these obstacles associated with conventional tablets. Fast disintegrating drug delivery systems are becoming more well-liked and accepted as innovative drug delivery methods in academia and industry because they are simple to use and improve patient compliance [6].

Fast releasing drug delivery systems such as orodispersible tablets (ODTs) or mouth dissolving tablets are the novel dosage forms which are suddenly disintegrates in saliva of the mouth region (1-3 min)

without the need of water and disperses rapidly before swallowing. ODTs are also known as mouth dissolving tablets, melt-in-mouth tablets, fast dissolving tablets and quick dissolving tablets [7]. Several methods have been reported for the preparation of ODTs which include tablet molding, spray drying, sublimation, lyophilization, solid dispersion, addition of disintegrants[8]. Direct compression is widely used technique for manufacturing of tablets particularly by the addition of dry binders, superdisintegrants and sugar-based excipients. Nowadays, this method is adopted in the preparation of ODTs containing potent active medicament with limited quantity of excipients to control the size of tablets [9]. Disintegration time is a significant role in the formulation ODTs which mainly depends on the nature and amount of disintegrating agent. Superdisintegrants plays the major role in ODTs is generally used at a low level in the solid dosage form, typically 1 – 10 % by weight relative to the total weight of the dosage unit. The disintegration efficiency is mainly based on the development swelling force followed by water absorption capacity when the tablet contact with dissolution medium to rapidly diffuses the micron size particles into bulk of the solution (saliva) [10]. Commonly used superdisintegrants are croscarmellose, crospovidone, sodium starch glycolate. The essential factor enabling rapid disintegration of ODTs tablets lies in the existence of a porous structure within the tablet matrix. Therefore, in order to create a porous matrix, volatile ingredients are incorporated which are subsequently subjected to a sublimation process [11]. Sublimation is a novel method for preparing fast dissolving tablets by the addition of a volatile salt mixing with other excipients to obtain a substantially homogeneous mixture which can be compressed as tablets. Then the compressed tablets are subjected to sublimation process, where the tablets were heated in hot air oven at 60^0C until constant weight was obtained to ensure the complete removal of volatilizable component [12]. Upon sublimation of volatilizable agents which creates highly porous tablets that significantly increases the surface area and rapid disintegration by swelling and breaking it into smaller particles, when the tablet comes in contact with saliva promoting faster drug release [13].

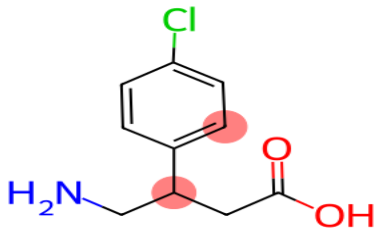


Figure 1: Chemical structure of Baclofen

Baclofen (BCF) is chemically 4-amino-3-(4-chlorophenyl)-butanoic acid ($C_{10}H_{12}Cl\ NO_2$) is a white crystalline powder with slightly bitter taste. It is slightly soluble in water, ethanol and practically insoluble in acetone. It rapidly dissolves in dilute mineral acids and dilute solutions of alkali hydroxides [14]. BCF is belonging to the BCS-III drug class, having low solubility and high permeability. BCF is a centrally acting skeletal muscle relaxant and antispastic drug used extensively in the treatment of for treating multiple sclerosis symptoms such as spasticity, stiffness and pain [15]. BCF is rapidly absorbed through the gastrointestinal tract following oral administration. About 70 to 80% of a dose is excreted unchanged in the urine. The peak plasma concentration reaches 0.5 to 3hrs after oral dose. The plasma elimination half-life of the drug is 2.5 to 4hrs and dosing frequency 2-3 times daily with dose range 5-15mg, maximum daily dose 100mg [16].

MATERIALS AND METHODS

Baclofen (BCF) was obtained as a gift sample from Gift sample from AKUMS Drugs & Pharmaceuticals Ltd, Haridwar, India. Crospovidone XL-10 and Sodium starch glycolate gift sample from Bioplus Life Sciences Pvt. Ltd, Hosur, Tamil Nadu. ISP Technologies, Inc. is providing gift sample of Plasdone K29/32. Ammonium bicarbonate, Camphor and Menthol were purchased from Fine Chemicals, Bengaluru. All other reagents and solvents used were of analytical grade satisfying pharmacopoeias specifications.

Determination of melting point

Melting point of baclofen was determined by capillary method. Fine powder of BCF was filled in a glass capillary tube (previously sealed at one end). The capillary tube was tied to thermometer and placed in the Thieles tube. The melting point and temperature range at that the drug melted was recorded.

Construction of standard calibration curve of BCF in pH6.8 buffer solution

The primary standard stock solution was prepared by dissolving 10mg of BCF in 10 ml pH 6.8 buffer solution to get concentration of 1mg/ml (1000µg/ml). Secondary stock solution was prepared by diluting 1ml of the primary stock solution with 10 ml pH 6.8 using buffer solution to get concentration of 0.1mg/ml (100µg/ml). The solution was subjected to scanning between 200-400nm in a UV-Visible spectrophotometerby using pH 6.8 buffers solution as blank [17]. The absorption maximum of BCF was obtained at λ_{max} 220nm.

Suitable aliquots of the secondary standard solution were transferred to a series of 10 ml volumetric flasks and the volume was made up to the mark using buffer pH 6.8 to get the concentrations of 2, 4, 6, 8 and 10µg/ml. The absorbance of these solutions was measured against pH 6.8 buffer solution as blank at 220nm by using UV-Visible spectrophotometer (Shimadzu 1800 Japan). The standard calibration curve BCF plotted by taking concentration on x-axis and absorbance on y-axis to obtain a straight line. The certain parameters such as the slope, intercept, coefficient of correlation, standard deviation was calculated.

FT-IR Spectroscopic Analysis: Drug polymer interactions were studied by FT-IR spectroscopy by using potassium bromide (KBr) press pellet technique. The pure drug and mixture of drug and excipients with

KBr (1:5) were compressed under 10 tones pressure in a hydraulic press to form a transparent pellet. The IR-spectrum of the pellet from 450-4000cm^{-1} was recorded taking air as the reference and compared to study any interference [18]. The resultant spectra of pure drug, excipients and physical mixtures were compared for any possible changes in the functional groups.

Differential scanning calorimeter (DSC): DSC was performed using DSC- 60 (Shimadzu, Tokyo, Japan) calorimeter to study the thermal behaviors of drug alone and mixture of drug and excipients. The analysis was performed at temperature 40-400^{0}C at the rate of 10^{0}C/min. Nitrogen gas was introduced at a pressure of 2 bars and a flow rate of 20ml/min and the data was analyzed by using TA-60 collector software [19].

Formulation of BCF orodispersible tablets:

Twelve batches of BCF orodispersible tablets were prepared by using sublimation method. The pre-compressed powder was prepared with various concentration of superdisintegrants such as crospovidone and sodium starch glycolate, sublimating agents viz camphor, menthol, and ammonium bicarbonate dry binder plasdone K29/32 and mannitol as diluents. All ingredients were accurately weighed and mixed in a poly bag. These powders were passed through sieve No. 60 ASTM (American Society of Testing and Materials) and then mixed in a large size poly bag using tumbling action. Finally, magnesium stearate and talc were mixed properly and compressed into 100 mg weight of tablets using a single-punch compression machine using 8mm flat round punches (Cadmach Ahmedabad, India) at 2-2.5 kg/cm^2 of hardness. After compression, the tablets were subjected to sublimation process by heated in a hot air oven at 60°C until constant weight was obtained to ensure the complete removal of volatilizable component [20]. Table 1 summarizes the batch details of BCF orodispersible tablets.

Table 1: Batch details of BCF orodispersible tablets

INGREDIENTS (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Baclofen	10	10	10	10	10	10	10	10	10	10	10	10
Camphor	5	10	15	20	25	30	-	-	-	-	-	-
Menthol	-	-	-	-	-	-	5	10	15	20	25	30
Ammonium bicarbonate	5	5	5	5	5	5	5	5	5	5	5	5
Crospovidone	2	4	6	8	10	12	-	-	-	-	-	-
Sodium starch glycolate	-	-	-	-	-	-	2	4	6	8	10	12
Plasdone K29/32	10	10	10	10	10	10	10	10	10	10	10	10
Magnesium stearate	1	1	1	1	1	1	1	1	1	1	1	1
Talc	1	1	1	1	1	1	1	1	1	1	1	1
Mannitol	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs
Theoretical weight of each tablet = 100mg												

Evaluation of formulated BCF orodispersible tablets

Micromeritics properties of pre-compressed powder: The flow characteristics of the different batches pre-compressed powder were measured by determining their angle of repose using fixed-base cone method. A glass funnel was secured with its tip positioned at a fixed height (H) above graph paper placed on a horizontal surface. The sample was poured through the funnel until the apex of the conical pile touched to the tip of the funnel. The height and radius of the heap was measured [21]. The experiment was repeated in triplicate, the angle of repose (tan θ) was calculated using the formula;

$$Angle\ of\ repose[\theta] = tan^{-1}(h/r)$$

h = cone height, r = radius of circular base formed by the powder on the ground.

The bulk and tapped densities of the pre-compressed powder were evaluated by using the bulk density apparatus. Known weights of formulated granules were transferred into a 50cc graduated measuring cylinder. The cylinder was fixed on bulk density apparatus and the timer knob was set for 100 tapings. Then, the initial bulk volume and final volume after 50 tapings were noted. The experiment was repeated in triplicate [21]. The respective densities of different batches of granules were calculated by using the following formulas;

Bulk density [gm/cc] = Mass of the sample (g)/Bulk volume (ml)

Tapped density[gm/cc] = Mass of the sample(g)/True volume (ml)

Compressibility index or Carr‟s index value of pre-compressed was computed according to the following equation;

$$Carr's\ index\ (CI\ \%) = \frac{Tapped\ density - Bulk\ density}{Tapped\ density} X100$$

Hausner‟s ratio of pre-compressed powder was determined by comparing the tapped density to the bulk density by using the equation;

$$Hausner's\ ratio = Tapped\ density / Bulk\ density$$

Weight variation, Hardness and Friability

The uniformity of weights of tablets was determined according to the method mentioned in Indian pharmacopeia. Weighed 10 tablets individually in an electronic balance and the average weight were determined. The standard deviation was calculated using the following formula;

Average weight (gm) = Total weight of the tablets /10

Standard deviation (%) = (Iw – Aw / Aw) x 100

[Where, Iw = Individual weight of the tablets, Aw = Average weight of the tablets]

For each formulation, the hardness of 10 randomly selected matrix tablets was examined using a Pfizer hardness tester (A-101 Secor India). The tablet hardness or crushing strength was measured in kg/cm^2.

The percentage of friability was evaluated by using Roche friabilator (USP EF-2 Electro Lab). Ten or twenty tablets from each batch were weighed and placed in the plastic chamber. The chamber rotated for 4 minutes or 100 revolutions. After 100 revolutions tablets were removed from the chamber and reweighed [21]. The percentage of weight loss or friability was determined by the following formula;

Friability (%) = Loss in weight of tablets / Initial weight x 100

Wetting time: This method will duplicate the *In-vivo* disintegration, as the tablet is motionless on the tongue. Wetting time was measured by placing a tablet on a piece of tissue paper folded twice and was placed in a small petri dish containing 6ml of simulated saliva pH 6.8, and the time for complete wetting was measured [22].

Water Absorption Ratio: A small piece of tissue paper folded twice was placed in a small petri dish containing water. A tablet was put on the paper and the time required for complete wetting was measured. The wetted tablet was reweighed. Water absorption ratio, R was determined by using following formula

$R=10(W_a - W_b)$ Where, W_b is the weight of tablet before water absorption, W_a is the weight of tablet after water absorption.

Drug content uniformity: Five tablets of each batch were weighed and powdered. The quantity of the powder equivalent to 10mg of BCF was suspended in 100 ml of phosphate buffer pH 6.8. The resulting solution was transferred into a stoppard conical flask and the flask was shaken for a period of 1hr by using a mechanical shaker at room temperature. The solution was filtered, after suitable dilution; the drug content in the filtrate was analyzed at λ_{max} 220nm using UV-Visible spectrophotometer (Shimadzu 1800 Japan) [23]. The obtained absorbance was plotted on the standard curve to get the exact concentration of the drug. Each experiment was carried out in triplicate (n=3). The actual drug content was determined by using the following relationship;

$$\text{Drug content} = \frac{(k \times \text{Absorbance} \pm B) \times \text{bath volume} \times \text{dilution factor}}{1000}$$

***In-Vitro* Disintegration studies:** The *In-vitro* disintegration time of a tablet was determined using digital double basket disintegration test apparatus (VTD-DV Veego Scientifics India). Place one tablet in each of the 6 tubes of the basket and the assembly should be raised and lowered between 30 cycles per minute in the pH 6.8 buffer solution, maintained at 37 ± 0.5^0C. The time in seconds was record for complete disintegration of the tablet with no palpable mass remaining in the apparatus.

***In-Vitro* Dissolution studies:** *In-vitro* dissolution studies of the promising Orodispersible tablets of BCF were performed according to USP XXIII Type-II dissolution apparatus employing a paddle stirrer at 50 rpm using 900 ml of pH 6.8 phosphate buffers at 37 ± 0.5^0C as dissolution medium. One tablet was used in each test. Aliquots of the dissolution medium (5ml) were withdrawn at specific time intervals (2, 4, 6, 8, 10, 15, 20 min) and replaced immediately with equal volume of fresh medium. The sample was filtered through 0.45µ membrane filter and diluted with appropriate dilution with respective medium. Then estimate the BCF concentration in the solution by using UV-Visible spectrophotometer (Shimadzu 1800, Japan) measured at λ_{max} 220 nm [24]. The absorbance of the samples was measured at different time intervals and the concentration, amount of drug released and the percentage of drug release were calculated by using PCP-Disso-V2 software.

Mechanism of drug release kinetics studies

The mechanism of drug release was determined by using PCP-Disso-V2 software. The *in-vitro* drug release drug release data of the formulations was analyzed with various kinetic equations like zero-order (% release v/s time), first- order (Log % retained v/s time), Higuchi matrix (cumulative % drug released vs. square root of time) and Korsemeyer and Peppas equation (Log cumulative percent drug released versus log time) [25]. The coefficients of correlation (r) values were calculated for the linear curves obtained by regression analysis of the respective plots.

Short term stability studies: The stability study of optimized formulation F6 was carried out for a specific time up to 60 days. The selected formulation was placed in self- sealing cover and stored at 5^0C, $25^0C/45\%$ RH and $40^0C/60\%$ RH for 60 days. After time period the formulation was observed that physical characteristics and analyzed for drug content for every 15days interval.

RESULTS

Melting points are often used to characterize organic and inorganic crystalline compounds and to ascertain their purity. The melting point of BCF was obtained in the range 208^0C. The characteristic absorption peak of BCF was obtained at 220nm. The obtained spectra represented in Figure 2.

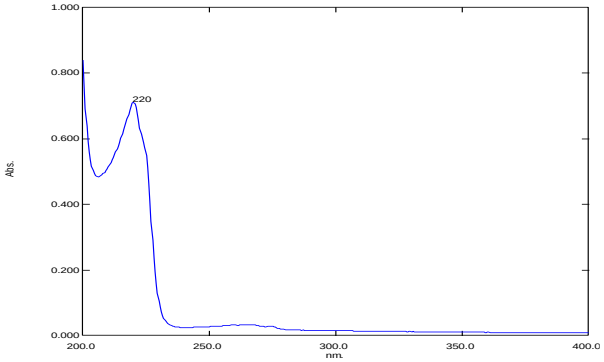


Figure 2: Absorption maxima (λ_{max}) of Baclofen in 6.8 pH buffer solution

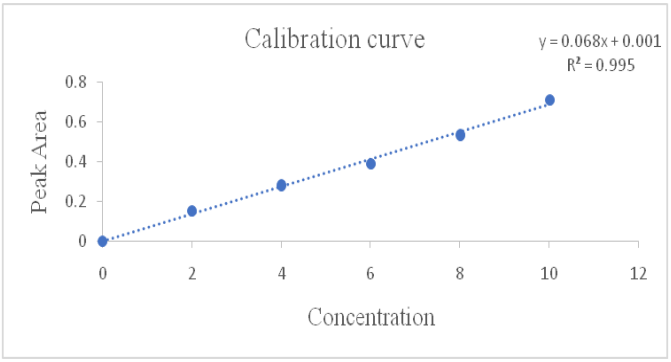
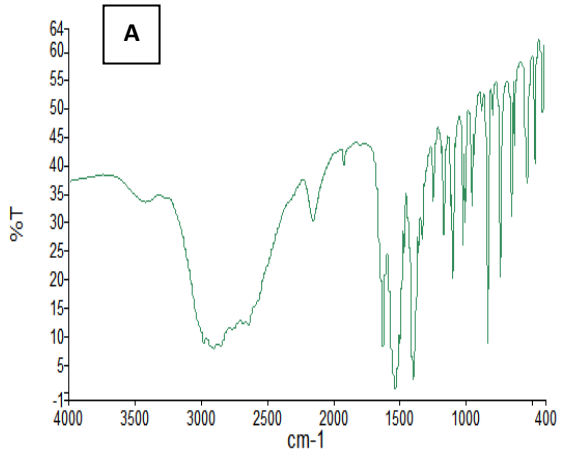
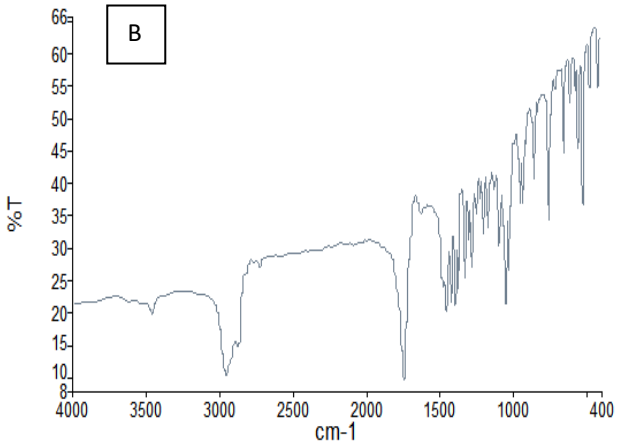
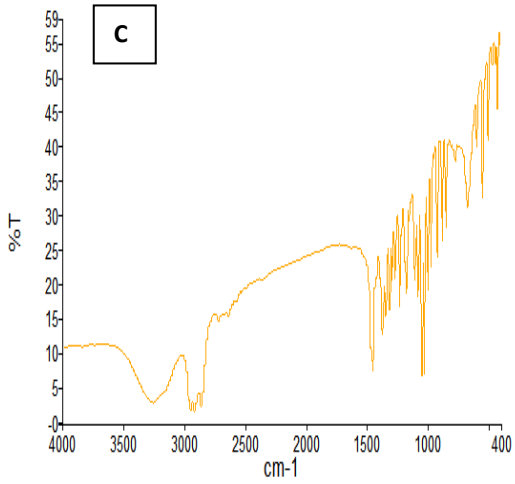
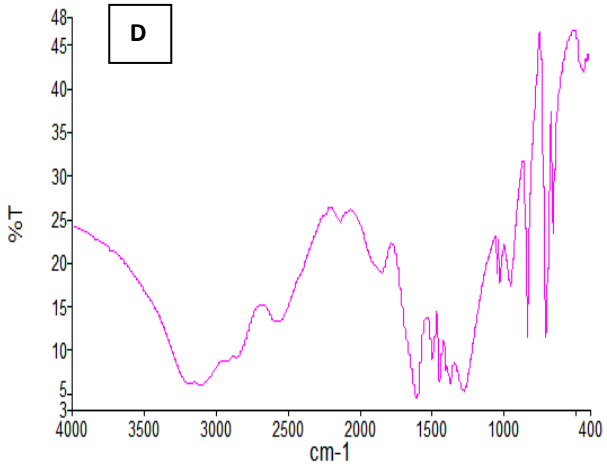


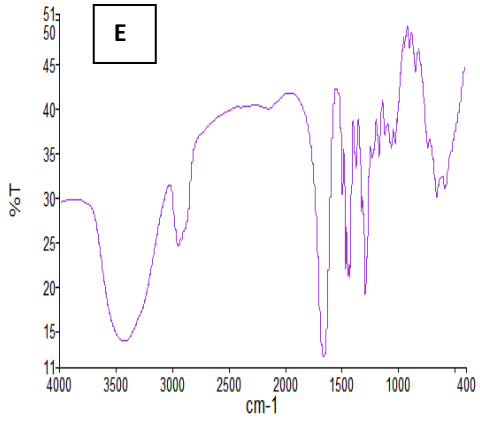
Figure 3: Calibration curve of Baclofen in pH 6.8 buffer solutions

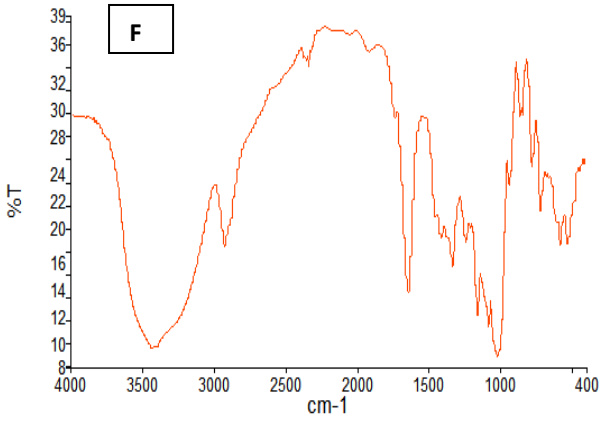












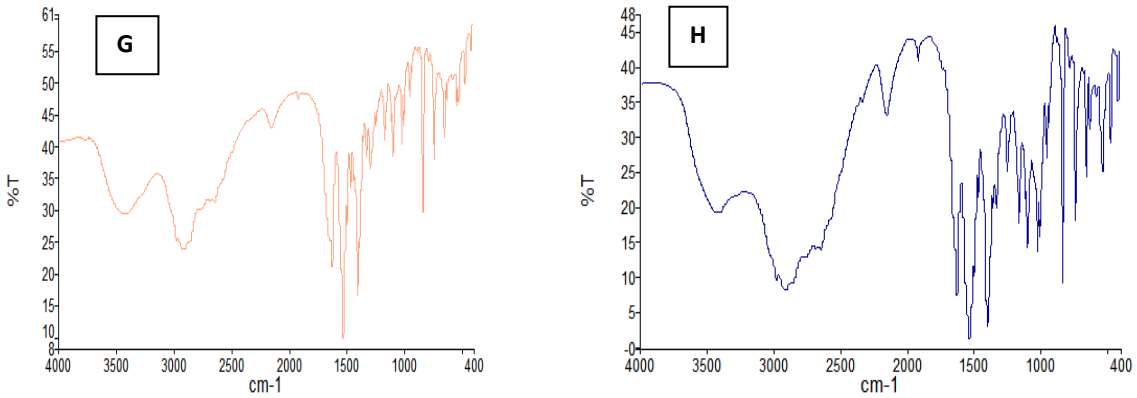


Figure 4: FTIR-Spectra of A) Pure BCF B) Camphor C) Menthol D) Ammonium bicarbonate E) Crospovidone F) Sodium starch glycolate G) Formulation F6 H) Formulation F10

FTIR spectroscopy was used to investigate the various functional groups of pure BCF and other excipients by KBr pellet technique. FTIR spectrum of pure BCF, camphor, menthol, ammonium bicarbonate, crospovidone, sodium starch glycolate and physical mixture of formulation (F6, F10) are shown in figure 4. The sharp major characteristic absorption peaks of BCF were exhibited at 3480cm^{-1} 2984.55cm^{-1}, 2490cm^{-1}, 1950cm^{-1}, 1510cm^{-1} corresponding to N-H$_2$, C-H O-H, C=O stretching and C=C blending (Fig.4a). The above exhibited sharp peak bands of pure BCF appears in the spectrum of optimized formulations (F6, F10) powder mixture (Fig 4g, h).

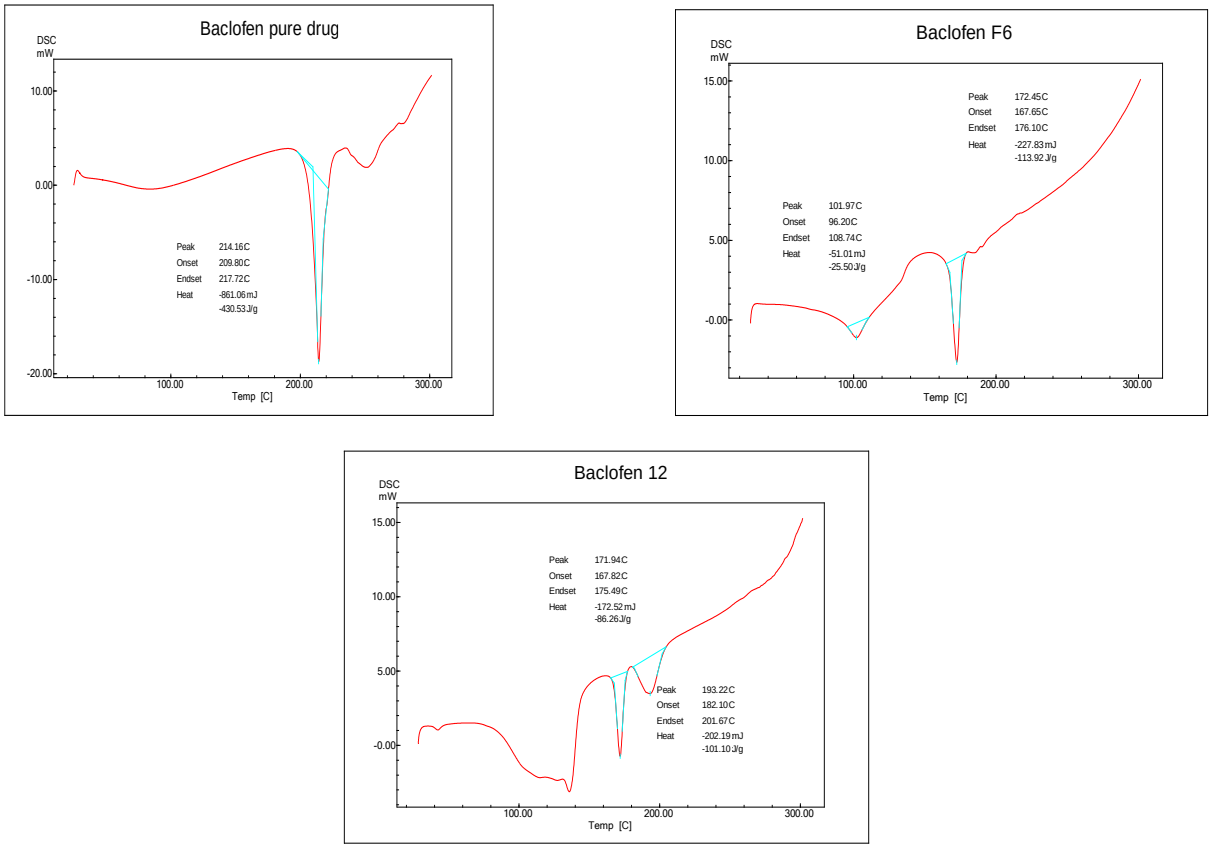


Figure: 5. DSC thermograms of BCF and Formulation F6 and F12

The DSC thermogram of pure baclofen showed a sharp endothermic peak at 214.50^{0}C, the formulation F6 and F10 showed a sharp endothermic peak at 172.14^{0}C. and 171.94^{0}C respectively (Fig. 5). The micromeritics properties such as angle of repose, bulk and tapped density, Carr's index, and Hausner's ratio of drug loaded pre-compressed powder blend of all the formulation (F1-F12) were determined by official methods. The investigated results were given in the Table 2.

Table 2: Micromeritics characteristics of pre-compressed powder of all the formulations

Formulations Code	Angle of Repose (θ)	Bulk Density(g/ml)	Tapped Density (g/ml)	Carr's Index (%)	Hausner's Ratio
F1	28.36	0.062	0.073	15.10	1.17
F2	28.16	0.060	0.070	14.68	1.16
F3	27.34	0.061	0.071	14.19	1.16
F4	27.99	0.064	0.073	12.64	1.14
F5	27.49	0.061	0.07	12.85	1.15
F6	26.30	0.064	0.072	11.11	1.13
F7	28.91	0.063	0.074	14.87	1.17
F8	27.68	0.065	0.076	14.48	1.16
F9	28.10	0.059	0.067	12.00	1.14
F10	27.11	0.064	0.075	14.66	1.17
F11	26.72	0.063	0.071	11.13	1.12
F12	26.89	0.062	0.070	11.43	1.13

Evaluation of formulated BCF orodispersible tablets

Baclofen ODTs were prepared by sublimation process and compressed using direct compression technique. All batches (F1 to F12) of tablets were investigate the various formulation variables such as weight variation, thickness, hardness, friability and the results are mentioned in Table 3.

Table 3: Post compression parameters of all formulations

Formulations Code	Average weight variation	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)
F1	96±0.52	2.30±0.03	2.2±0.1	0.887±0.002	98.47
F2	98±0.54	2.29±0.05	2.1±0.3	0.762±0.001	98.43
F3	99±0.48	2.30±0.08	2.3±0.2	0.798±0.003	98.56
F4	96±0.25	2.31±0.08	2.1±0.3	0.625±0.004	95.73
F5	98±0.29	2.33±0.04	2.4±0.1	0.658±0.002	97.54
F6	99±0.68	2.22±0.08	2.4±0.1	0.547±0.006	99.58
F7	98±0.47	2.32±0.05	2.2±0.2	0.679±0.004	98.54
F8	96±0.26	2.26±0.08	2.3±0.1	0.665±0.002	97.60
F9	95±0.36	2.28±0.06	2.4±0.1	0.654±0.006	98.28
F10	94±0.78	2.29±0.07	2.3±0.2	0.598±0.004	98.85
F11	96±0.26	2.32±0.09	2.4±0.1	0.611±0.005	98.16
F12	94±0.36	2.22±0.09	2.3±0.2	0.602±0.004	99.87

Average of 3 determinations, ±SD

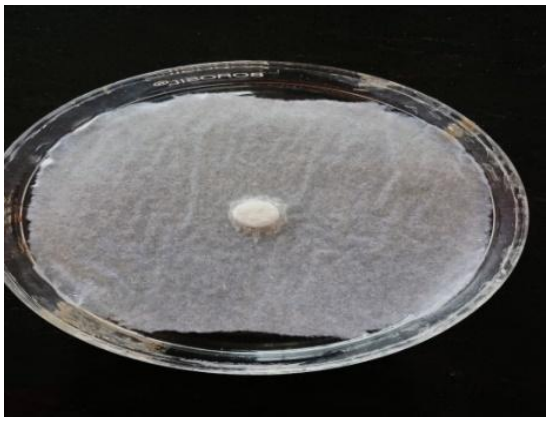


Figure 6: Wetting of ODT

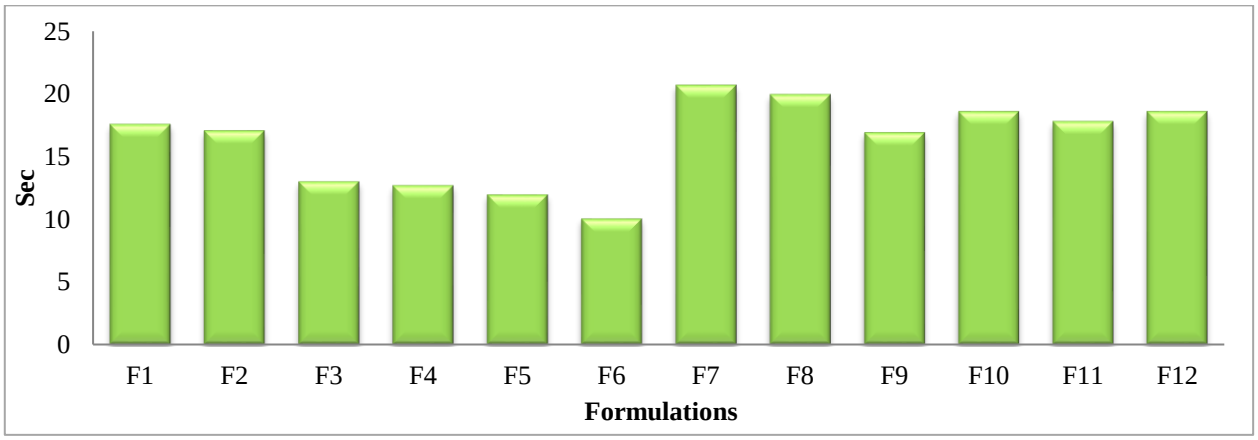


Figure 7: Wetting time of all formulations

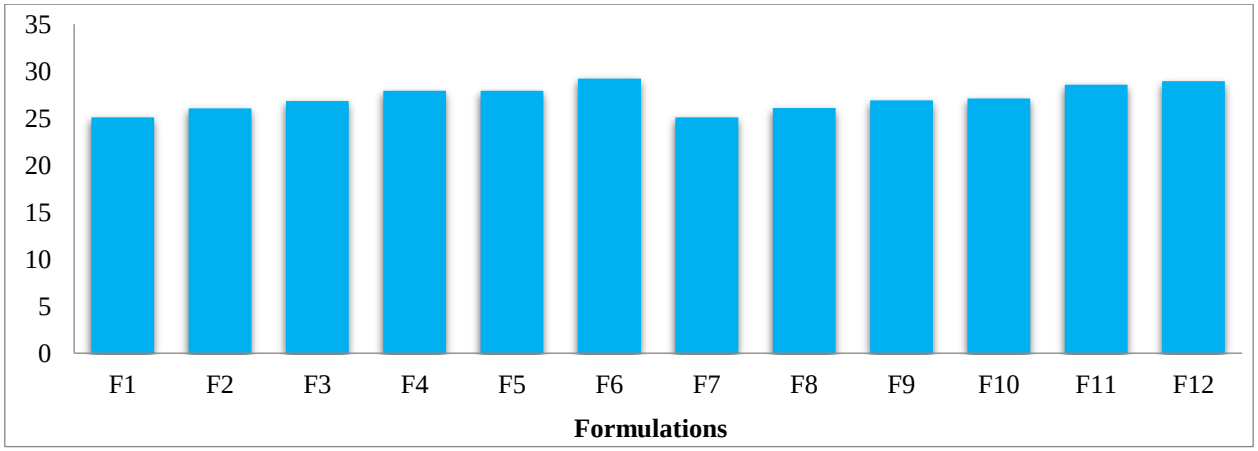


Figure 8: Water absorption ratio of all formulations

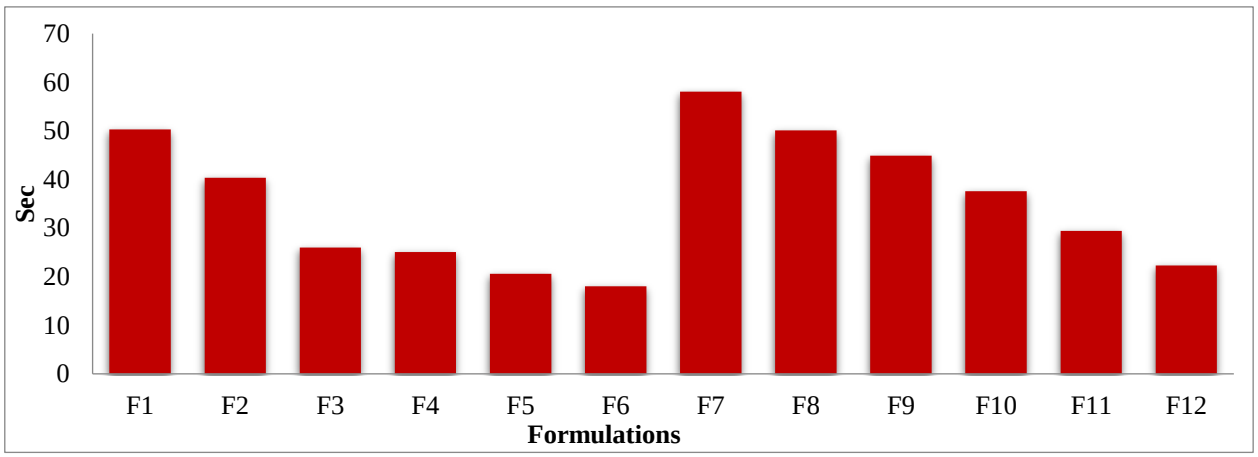


Figure 9: *In-vitro* disintegration time of all formulations

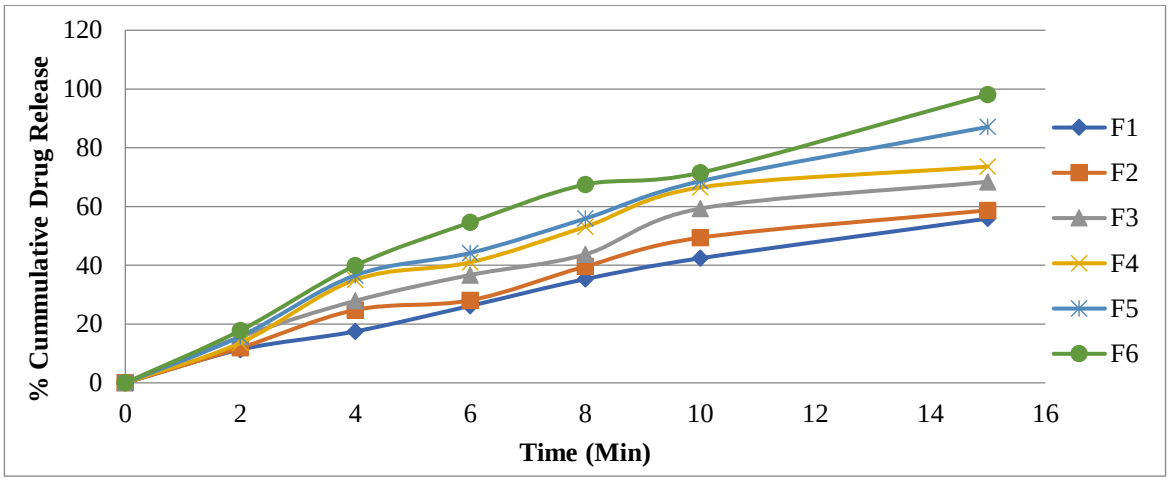


Figure 10: *In-vitro* drug release profile of formulations F1-F6

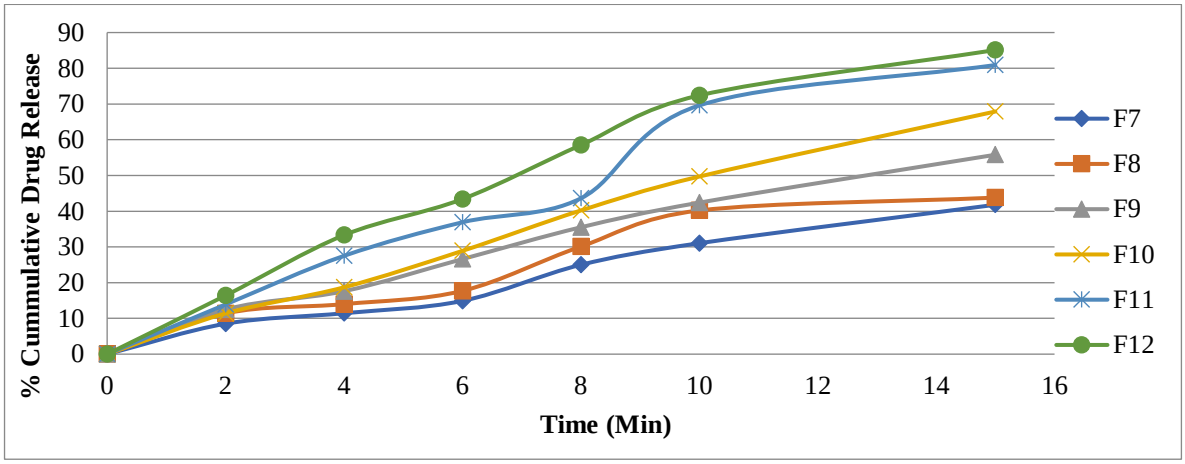


Figure 11: *In-vitro* drug release profile of formulations F7-F12

The data obtained from the *in-vitro* dissolution studies was subjected to kinetic treatment to obtain the order of release and best fit model for the formulations by using PCP-Disso-V2 software. The R^2 values obtained in each kinetic model for all the formulated tablets are presented in Table 4.

Table 4: Kinetic drug release of optimized formulation (F6) BCF orodispersible tablets

Kinetic models	R^2 Values	N-Values	Best fit model
Zero-order	**0.9502**	-	
First order	**0.9412**	-	
Hugachi matrix	**0.9816**	-	
Korsemeyer-Peppas	**0.9852**	**0.7632**	Peppas

Table 5: Short term stability studies of optimized formulation F6

Sampling interval	Drug content (%)			Physical characters		
Days	**5⁰C**	**25⁰C/45%RH**	**40⁰C/60%RH**	**Colour**	**Odour**	**Taste**
0	99.58	99.58	99.58	No changes	No changes	No changes
15	99.58	99.58	99.58	No changes	No changes	No changes
30	99.51	99.58	99.56	No changes	No changes	No changes
45	98.95	99.52	99.55	No changes	No changes	No changes
60	98.68	99.13	98.86	No changes	No changes	No changes

DISCUSSION

Spasticity is a condition of abnormal muscle tightness due to prolonged muscle contraction associated with common neurological disorders like multiple sclerosis, stroke, cerebral palsy and spinal cord injury. BCF is a novel drug acting as skeletal muscle relaxant prescribed for this indication to relief pain and muscular spasticity. Absorption of the BCF is limited to stomach or upper part of the GI tract [25]. To improve the stability of BCF under gastric condition and bioavailability can be increased by making the drug completely absorbed in the stomach by orodispersible drug delivery system. The melting point (MP) determination is a key tool used in the formulation research and development as well as in quality control in various industry segments to identify and check the purity and thermal behavior of the active drug. In the present investigation the M.P of BCF was found to be 208^{0}C. There are no changes in melting range of the drug as mentioned in standard drug specifications. Therefore, the drug BCF is in pure form and suitable in the manufacturing process. The absorption maxima and standard calibration curve of BCF in pH 6.8 were subjected to scanning in the range of 200-400nm using double beam UV-Visible spectrophotometer. The characteristic sharp absorption peak was obtained at 220nm (Figure 2). The present analytical method obeyed Beer-Lambert's law in the concentration range of 2-10 µg/mL. The linear regression equation was generated in pH6.8 ($y=0.068x+0.001$, $R^2=0.9998$). The selected method was found to be sensitive, accurate, precise and reproducible and used for the estimation of BCF in the formulation (Figure 3). The IR spectra's individual polymer and physical mixtures of formulation were compared with the spectra of the pure drug BCF suggests that the major peaks for drugs are obtained as nearer value and there were no considerable changes in IR peaks. Hence, there is no any interaction between the drug and excipients which are also indicate the drug was molecularly dispersed in the polymers or in formulation (Figure 4). The analytical technique of DSC was frequently used to study melting behavior, thermal stability, crystallization, solid-state polymorphic transitions and chemical interactions of the drug during manufacturing process. By observing the thermograms of pure drug and physical mixture of formulation were suggest that there is no thermal transition or interaction.

The investigation of pre-compressed characteristics such as flow properties, bulk and tapped density, carr's index, compaction of powder blend was important because which are influences the physical properties of in the tablet. All the investigated results were obtained in the acceptable range.

The uniform size and shape of the tablet to tablet is control by thickness and diameter of a tablet which are impacts on disintegration and dissolution behaviors and dose uniformity. The thickness of formulated tablets was obtained in the acceptable range between 2.22-2.33mm (Table 3). The weight variation of the tablets was observed within the limit ±7.5% and shows the uniformity of weight with low standard deviation value. The hardness of all the formulations was ranging from 2.0-2.3 kg/cm^2 reveals that the tablets are good mechanical strength and in acceptable range (Table 3). Friability is a significant factor to be considered to assess the mechanical strength of tablets and their ability to withstand handling, packaging, and transportation without breaking or crumbling. The friability of the tablet was found in the range of 0.547 – 0.887 %. The results reveals that the formulated tablets shows good mechanical resistance and within the limit of official monograph (>1). Drug content uniformity is one an important test to ensure the consistency of active medicament present in each tablet in a given batch should be remains within specified acceptance limits. The drug content of tablets (F1-F12) were evaluated by using UV-Visible spectroscopy in pH 6.8 buffer solution and are found to be in the range of 95.73 to 99.87%w/w (Table 3) indicating that the drug is uniformly distributed in each tablets ensuring the dose uniformity. In general, ODTs are placed in the oral cavity, quickly melt in saliva and rapidly disperse before swallowing. Wetting time is a critical parameter to determine the behavior of superdisintegrants in ODTs when contact with saliva or water medium before disintegration. The wetting time of the formulated tablets (F1-F12) were found to be in the range 10.03 to 20.69 sec (Table 3). Further, wetting time was significantly affected by the hydrophilicity of the superdisintegrants when the tablet bed contact with water or saliva becomes to swell causes small pores and increasing the wetting time. Swelling capacity of superdisintegrants in the ODTs was observed in pH 6.8 buffer solutions as water absorption ratio and lies in the range between 25.31 – 29.20%w/w. The results suggest that the concentration of superdisintegrants in the formulation was directly proportional to the water absorption ratio. The optimization of disintegration time is most important for the development of ODTs, in most cases a tablet that dissolves or disintegrates quickly in the oral cavity upon contact with saliva to form dispersion which can be entering into systemic absorption site. The formulation batches F1-F6 containing various concentration of crospovidone was noticed in the range of 50.26, 40.35, 25.98, 25.03, 20.60, 18.02 sec. It was observed that the high level of crospovidone in the tablet shows very shorter disintegration time due to non-ionic, cross-linked polyvinylpyrrolidone moiety swells quickly upon contact with liquid creates a rapid capillary action, faster hydration and little tendency of gel formation which promotes the fast disintegration of tablet. Further, the various concentration of camphor serves as a sublimating agent in the formulation (F1-F6) owing to vaporizes during the sublimating process to create porous structures in the tablet surface, facilitating rapid disintegration. The batches of F7-F12 formulated tablets show the disintegration time 58.03, 50.06, 44.89, 37.60, 29.39 and 22.30 sec respectively. Results reveal that sodium starch glycolate involves rapid swelling significantly in the presence of water, to forming a thick gel matrix layer on the boundary surface of tablets that hindered the flow of water followed by decreasing disintegration time of tablets evenly. Moreover, the tablets prepared by various concentration of menthol to

form small rigid pores after sublimation which are may decrease the disintegration of tablets. The ammonium bicarbonate utilized as a sublimating aid or porosity forming agent at a concentration 5%w/w in the tablets. After sublimation the volatile component of ammonium bicarbonate gives dual effect on the tablet disintegration and dissolution. When subjected high temperature and pressure, sublime slowly resulting high porous structure which are helps to rupture the tablet quickly by the generation of carbon dioxide bubbles in the presence citric acid of salivary juice followed by faster dissolution.

The *In-vitro* drug release study was conducted by USP XIII rotating basket apparatus, (Model-TDT-08L, Electro lab Mumbai, India) using pH6.8 buffer solution as dissolution medium. The percentage of drug release from the formulated tablets F1-F6 was obtained in the range of 55.80 to 98.94% w/w and F7-F12 was shows in the range of 41.80 to 85.11%w/w at the end of 15min time period (Fig 10, 11). Thus, formulation F6 showed 98.94% w/w drug release at the end of 15 min which contains crospovidone (12%) as superdisintegrants and camphor (30%) as sublimating agent. The high wicking action of crospovidone which allows water regularly into the tablet and camphor upon sublimation which was developing highly porous structure that predominantly increases the effective surface area followed by faster drug release at the site of action.

Different models were adopted for fitting the drug release data in best fit kinetic modeling using PCP-Disso-V2 software. The drug release profile of optimized formulation batch F6 was follows the Peppas model which indicated a non-Fickian diffusion drug release mechanism. This is likely due to the interplay of rapid disintegration and diffusion to form a uniform dispersion drug in the bulk of the dissolution medium or salivary water (Table 4).

The optimized formulation F6 BCF orodispersible tablets were subjected to conduct short term stability studies according to the ICH for zone IV in the desiccators with saturated salt solution. The physicochemical parameters, drug content was determined after 15-, 30-, 35- and 60-days period and there are no any significant changes in the physical appearance and drug content. Therefore, the formulated BCF orodispersible tablets have good stability at mentioned humidity and temperature conditions (Table 5).

CONCLUSION:

In the present research work, BCF orodispersible tablets were successfully manufacturing direct compression technique followed by sublimation process and investigated the potential utility of superdisintegrants such as crospovidone and sodium starch glycolate and sublimating agents like camphor, menthol and ammonium bicarbonate. All the pre-compressed parameters were in acceptable limits. The sublimed tablets containing camphor and crospovidone gives an excellent effect on post compressed parameters such as wetting time, drug content, *In-vitro* disintegration and dissolution. Optimized formulation batches F6, containing crospovidone and camphor, showed the fastest disintegration time (<18 sec) and highest percentage of drug release followed a non-Fickian diffusion mechanism. Finally, conclude that the sublimation process is a novel technique adopting after the compression of tablets was suitable for the development of orodispersible tablets BCF to promote quick relief of muscular pain in short period of time. We recommended to further investigation of the critical manufacturing variables by using pilot plant scale-up techniques and involving their suitability for long time application, shelf-life stability, *Invitro-Invivo* correlation (IVIVC), determination of bioavailability and clinical investigations be necessary to improve the therapeutic efficacy and patient compliance.

Acknowledgement: The authors thank AKUMS Drugs & Pharmaceuticals Ltd, Ranipur, Haridwar, India to providing gift sample of Baclofen. We are very thanking to the Principal, Chairman of Togari Veeramallapa Memorial College of Pharmacy, Ballari, Karnataka.

Conflict of Interest: The authors declare no potential conflict of interest with respect to the contents, authorship, and/or publication of this article.

Author Contributions: All authors have equal contribution in the preparation of manuscript and compilation.

Source of Support: Nil

Funding: The authors declared that this study has received no financial support.

Informed Consent Statement: Not applicable.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

Ethical approval: This study does not involve experiments on animals or human subjects

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