International Journal of Pharmacy and Biological Sciences
ISSN: 2321-3272 (Print), ISSN: 2230-7605 (Online)
IJPBS™ | Volume 8 | Issue 4 | OCT-DEC | 2018 | 915-926
Research Article | Pharmaceutical Sciences | Open Access | MCI Approved| ज्ञान-विज्ञान विमुक्तये
|UGC Approved Journal |

PREPARATION AND *INVITRO* EVALUATION OF HIGHLY POROUS GASTRORETENTIVE FLOATING BECLOMETHASONE DIPROPIONATE TABLETS

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ABSTRACT

The present study is aimed to formulate floating gastro retentive (GR) tablets containing beclomethasone dipropionate using a sublimation material for prolongation of gastric residence time. Three different ratios of hydroxyl propyl methyl cellulose (HPMC) K4M is used in three different methods for the preparation of tablets. In this case, the drug release from tablet was highly dependent on the polymer concentrations. Camphor, the sublimation material is used in the preparation of GR tablets. Camphor changes to pores in the tablet during the sublimation process. As the camphor gets sublimed, floating properties and density of tablets were affected by the sublimation of camphor. Gastro retentive floating beclomethasone dipropionate tablets which were prepared floated for over 24 hrs and had no floating lag time. Therefore, as the concentration of camphor in the tablet matrix increases, the hardness of the tablet decreased after sublimation. Release profiles of the drug from the GR tablets were not affected by tablet density or porosity.

KEY WORDS

Beclomethasone Dipropionate, gastro retentive floating tablets, HPMCK4M, sublimation method.

INTRODUCTION

The principle and more advisable route for delivering a drug is the oral route, but in case of physiological variability like gastro intestinal transit and GRT there is a major problem. The controlled oral drug delivery of GRT is always less than 12h, and it plays a vital role in complete dosage form transit [1, 3]. These characteristics lead to evolution of a drug delivery system that retains in the stomach for a prolonged and predictable time [2].

Floating drug delivery systems (FDDS) have low bulk density than that of gastric fluids. Due to their lower densities, FDDS float above the gastric content without effecting gastric emptying rate for longer duration of time and it provides controlled release of drug [3]. These systems have been extensively used because there are no interactions in relation to the motility of the GIT and a large number of floating dosage forms commercialized and marketed worldwide. Two systems have been used in the development of FDDS, on the basis of mechanism of buoyancy. They are effervescent systems and non-effervescent system In Effervescent systems effervescent substances like carbonate/ bicarbonate salts and citric / tartaric acids are used to liberate Co_2. The liberated Co_2 is entrapped in the jellified hydrocolloid layer of the systems thus specific gravity is decreased and it is made to float above gastric content [4, 5].

In Single Layer Floating Tablets or Hydrodynamically Balanced System (HBS), Co_2 generating agents and the drug were mixed thoroughly within the matrix tablet to produce a formulation. And to remain buoyant in the stomach without effecting the gastric emptying rate for a prolonged period of time. The drug is released slowly at a desired rate [6, 8]. When the drug is completely released the system is expelled out from the stomach

which leads to an increased GRT and better control over fluctuation in plasma drug concentration [7, 10]. In Sublimation System, Camphor is used as a sublimation material. It is sublimated into the tablet matrix, forming pores in the matrix above the sublimation temperature. This system is useful to develop a porous floating matrix tablet using the sublimation method [11].

Beclomethasone dipropionate is the dipropionate ester of synthetic glucocorticoids possessing anti-inflammatory and immunomodulating properties. Medically it is used as steroid. It acts as a prodrug for the free form, beclomethasone (INN). Various available forms of it include inhaler (long term management of asthma), cream (dermatitis and psoriasis), pills (ulcerative colitis), and nasal spray (allergic rhinitis and nasal polyps) [12, 13]. Orally it is used to treat mild to moderate Crohn's disease of ileal or ileal right colonic localization Topical application of it is helpful to treat mild to moderate graft versus host disease**.** And it has a biological half-life 2. 8hrs.The aim of the present work is to prepare the gastro retentive floating tablets by using different concentrations of polymer using different methods by direct compression method and analyzing the release of drug from the tablets which is dependent on the concentration of polymer HPMC K4M. The main aim of present work is to prepare and evaluate highly porous gastro retentive floating tablets of Beclomethasone dipropionate [14, 15].

MATERIALS AND METHODS

Materials

Beclomethasone dipropionate is a gift sample from Halmak Pharmaceuticals Pvt.LTD, Ameerpet, Hyderabad, Hydroxy Propyl Methyl Cellulose K4M from Research Lab fine chem. industries, Mumbai, Micro Crystalline Cellulose from NR Chem., Bombay, Sodium bicarbonate from S.D Fine Chem. LTD, Mumbai, Magnesium stearate from KEMPHASOL-Bombay, Lactose from Qualikems Fine Chem. Industries, Mumbai, Talc from NICE Chemicals Private LTD.

Methods

Preparation of gastro retentive floating tablets is done using three different methods for each method three different formulations were prepared at different ratios. The methods include: Effervescent method, non-effervescent method and Sublimation method.

Direct compression method is used for preparation of tablets in all the three methods and mixing of powder was carried out in a blender for 15min followed by addition of magnesium stearate, lactose, and talc further mixed for 5min [1, 2, 16].

Effervescent method

In this method 10mg of BD, polymers such as HPMC K4M, MCC were used in three different ratios, 15mg of lactose as glidant, 5mg of magnesium stearate as lubricant, sodium bicarbonate acts as effervescent agent and citric acid as preservative were taken for tablet preparation.

Non-effervescent method

In this method 10mg of BD, polymers such as HPMC K4M, MCC were used in three different ratios, 15mg lactose as glidant, 5mg magnesium stearate as lubricant were taken for the preparation of tablets.200mg of tablet was prepared in effervescent and non-effervescent method.

Sublimation method

To the formulation prepared by non-effervescent method addition of 100mg camphor is done. Camphor acts as sublimation material and weighed 300mg for each tablet fed manually into the die of an instrumented single punch tableting machine and directly compressed to make one tablet. Sublimation method formulated tablets were sublimated at 60^0C in hot air oven and the tablets weight were measured at regular intervals of time, camphor should be sublimated within 24 hrs completely. [1,2]

Table.1 formulation of beclomethasone dipropionate floating tablets using effervescent method

Ingredients	F1 (1:5)	F2 (1:6)	F3 (1:7)
BD	10	10	10
HPMC(K4M)	50	60	70
MCC	15	25	35
NAHCO3	90	80	70
citric acid	15	15	15
Mg Stearate	5	5	5
Talc	10	10	10
Lactose	15	15	15

Table.2 formulation of beclomethasone dipropionate floating tablets using non-effervescent method

Ingredients	F4 (1:5)	F5 (1:6)	F6 (1:7)
BD	10	10	10
HPMC(K4M)	50	60	70
MCC	110	100	90
mg stearate	5	5	5
Talc	10	10	10
Lactose	15	15	15

Table.3 formulation of beclomethasone dipropionate floating tablets using sublimation method

Ingredients	F7 (1:5)	F8(1:6)	F9(1:7)
BD	10	10	10
HPMC(K4M)	50	60	70
MCC	110	100	90
mg stearate	5	5	5
Talc	10	10	10
Lactose	15	15	15
Camphor	100	100	100

Evaluation tests

Floating ability

The floating ability of single tablet was determined with 500 ml pre-warmed 0.1 N HCl solution and shaken at 70 rpm, 37 ± 0.2°C for 24 h, using a shaker apparatus.

Floating properties of tablets

In a 100 ml glass beaker 0.1 N HCl is taken to that solution tablets were added.

Floating Lag Time: The time required for a tablet to float on the surface of the medium is floating lag time.

Floating Duration Time: The duration of time where tablet remained floating on the medium surface was determined as floating duration time.

Precompression parameters

Precompression parameters were studied before punching a tablet.

Bulk density: It is the ratio of the known mass of the powder sample which is untapped and its volume including interparticulate void volume.

$$\text{Bulk density} = \frac{\text{Mass of the powder}}{\text{Bulk voume of the powder}}$$

It is measured in gm/ml.

Tapped density: It is the ratio of the mass of the powder to the volume occupied by the powder after a fixed number of taps.

$$\text{Tapped density} = \frac{\text{Mass of the powder}}{\text{Tapped volume of the powder}}$$

It is measured in gm/ml.

Compressibility index

$$\text{carrs index}\% = \frac{\text{tapped density} - \text{Bulk density}}{\text{Tapped density}} \text{ x } 100$$

Hausner's Ratio

$$\text{Hausner Ratio} = \frac{\text{tapped density}}{\text{bulk density}} \text{ x } 100$$

Angle of Repose: It is the minimum angle at which any piled up bulky or loose material stands without falling down. The angle of repose ranges from 0^0 to 90^o.

The tangent angle of repose (θ) was calculated by an equation [1,2,16]

Tan θ = h/r

Angle of repose (θ) = tan-1(h/r)

Where,

h=height of the pile, r=radius of the pile, θ=angle of repose.

Drug-excipient (DE) interactions

FTIR: This is used to study the physical and chemical interactions between the drug and excipients used in the dosage form.

Differential Scanning Calorimeter (DSC): It determines the temperature and heat flow and also material transitions as a function of time and temperature.

Post compression parameters

Weight variation: Variations in weight were tested in randomly selected 20 different tablets from every batch. Digital electronic balance (Citizon CG203, India) is

used for measuring weight variations. Then individual tablets were weighed and compared with an average weight. Weight values were reported in mg. Mean and SD were calculated.

Hardness (or) tablet crushing strength: The resistance of the tablets to capping, abrasion or breakage during storage, transportation and handling before usage depends on its hardness. Tablet hardness is the amount required to crush or fracture a tablet kept on its edge. Monsanto type (Make: Singhala) hardness tester is used for testing hardness. This instrument measures the crushing strengths.

It is measured in kg/cm^2.

Thickness: The diameter and thickness of the tablets were measured for 20 tablets from each formulation. Digital Vernier caliper is used for this study and it gives accurate measurements and information about variation between tablets. It is measured in mm.

Friability (F): Friability of the tablet is determined using Roche friabilator. Preweighed 20 tablets were subjected to the combined effect of abrasion and shock in a Friabilator containing a plastic chamber revolving at 25 rpm up to 100 revolutions. Remove the dust using soft muslin cloth, and then tablets were re-weighed, and friability percentage was calculated using the following formula

$$\%\text{Friability} = \frac{\text{Tablet weight before friabilty} - \text{Tablet weight after friability}}{\text{Tablet weight before friabilty}} \text{ x } 100$$

Swelling Index: Individual weights of the floating tablets were taken (W0) and separately placed in a glass beaker which contains 200 ml of 0.1 N HCl or 50ml of water and incubated at 37°C ± 1°C. At regular 1-hr time intervals until 24 hrs, they were removed from beaker, and by using a tissue paper excess liquid on the surface was removed carefully. The swollen floating tablets were then re-weighed (Wt). The percentage of swelling index is given as

$$\% \text{ Swelling index} = W_{wet} - W_{dry} / W_{dry} \text{ x } 100$$

***Invitro* Dissolution Study:** The release of beclomethasone dipropionate from the floating tablets was determined by using USP II paddle type dissolution test apparatus. This test is performed using 900 ml of 0.1 N HCl solution at 37 ± 0.5 °C and the paddles were rotated at 50 rpm. At regular time intervals, 5ml aliquot is withdrawn from the dissolution medium and it is replaced with fresh medium to keep the constant volume. The samples taken in aliquots were filtered and diluted with suitable concentrations of 0.1 N HCl. The absorbance was measured at 239 nm.

Kinetic Analysis of Dissolution Data

Zero order kinetics

$f_t = k_o t$

Where $f_t = 1 - (W_t / W_0)$ and ft represents the fraction of drug dissolved in time t .

First order kinetics

$\text{Log } Q_t = \text{Log } Q_0 + K_1 t/2.303$

Where Q_t is the amount of drug released at time t

Korsmeyer Peppa's model

$Q_t/Q\alpha = K_k t_n$

Where K_k is a constant and n is the release exponent that indicates drug release mechanism it is shown in Table

Table.4 various mechanisms of drug transport

Release exponent(n)	Drug transport mechanism	Rate,the function of time
0.5	Fickian diffusion	$t^{-0.5}$
0.5<n<1.0	Anomalous transport	t^{n-1}
1.0	Case-II transport	Zero order release
Higher than 1.0	Super Case-II transport	t^{n-1}

Higuchi Model

$Q_t = K_H$ t 1/2

A linear relationship between the square root of time versus the concentration implies that the drug release follows Fickian diffusion mechanism [1,2,16].

RESULTS AND DISCUSSION

Table.5 calibration curve of beclomethasone dipropionate

Concentration µg/ml	Absorbance
10	0.013
20	0.024
30	0.035
40	0.046
50	0.056
60	0.065
70	0.077
80	0.087
90	0.099

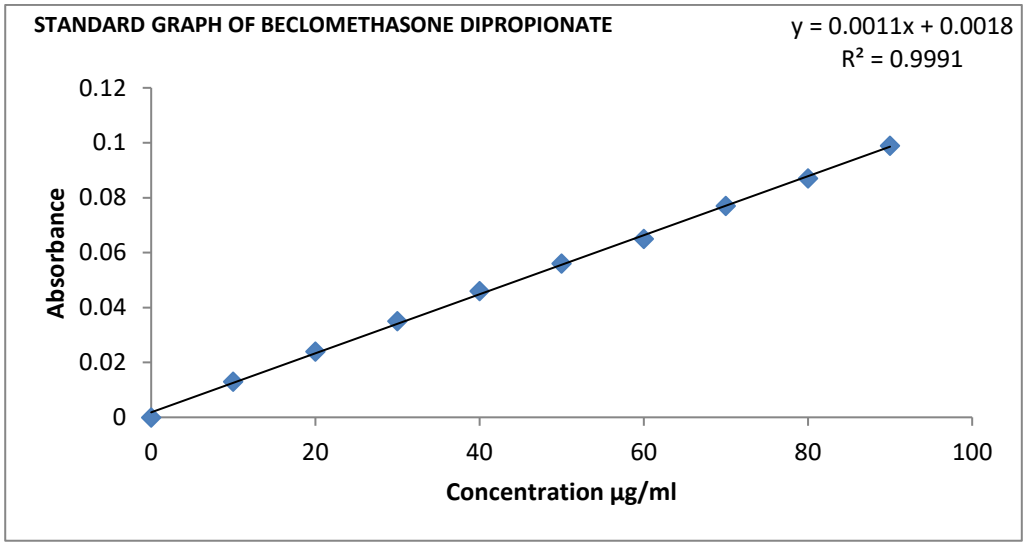

Figure.1 Standard calibration curve of pure beclomethasone dipropionate

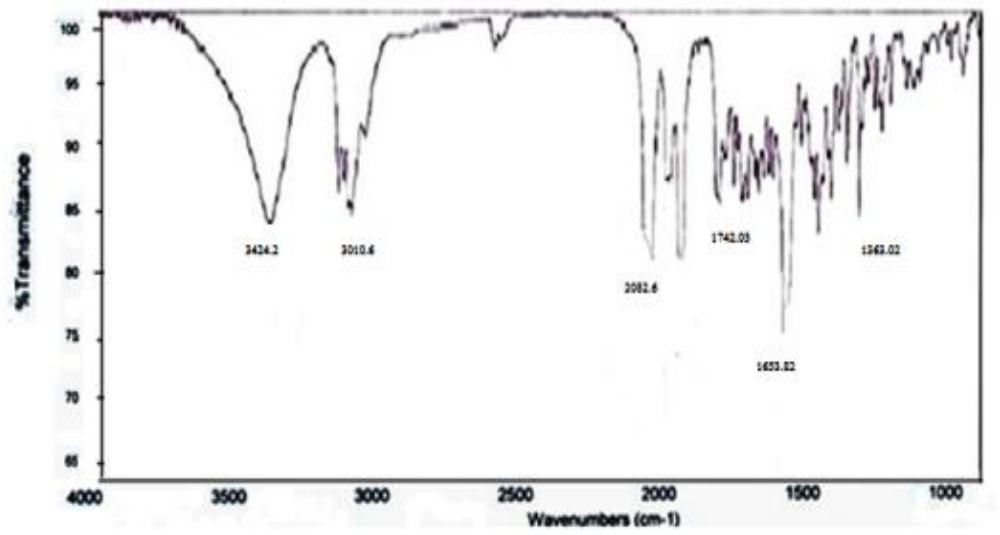

Figure.2 FTIR spectra of pure beclomethasone dipropionate

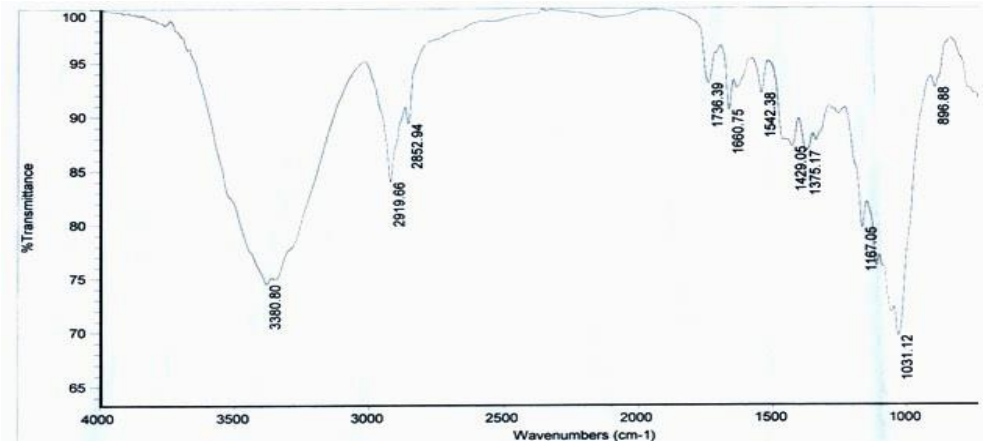

Figure.3 FTIR spectra of beclomethasone dipropionate gastro retentive floating tablets

Table.6 Interpretation of beclomethasone dipropionate and optimized formulation

Frequency of pure drug	Frequency of optimized drug	Frequency ranges	Functional group
3271	3380	3650-3200	Alcohol O-H
1730	1736	1735-1750	Aldehyde C=O
1654	1660	1650-1690	Amide C=O

It ensures that there is compatibility between pure drug and the optimized formulation

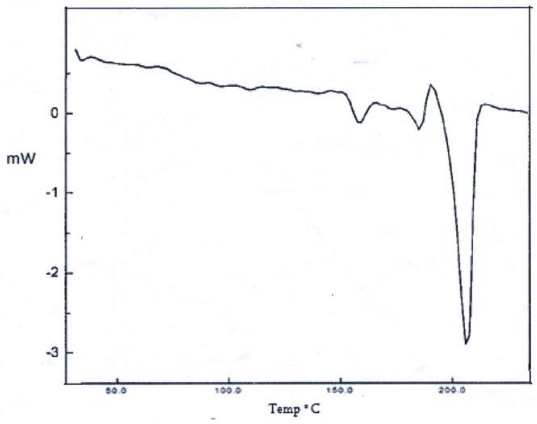

Figure.4 DSC of pure beclomethasone dipropionate

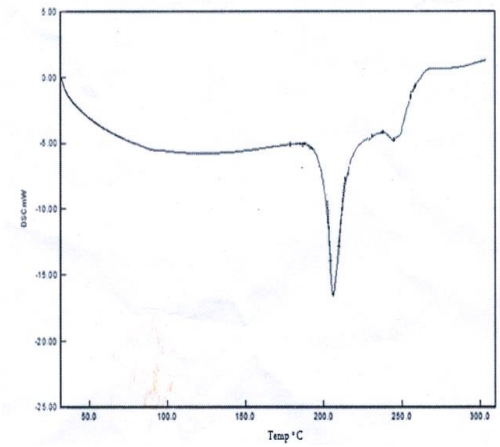

Figure.5 DSC of beclomethasone dipropionate floating tablets

Selected formulations of Gastro retentive floating tablets of Beclomethasone dipropionate were characterized for DSC. The pure Beclomethasone dipropionate showed a sharp endothermic peak at 213° C. Similar endothermic peaks were observed at similar temperature in the prepared Gastro retentive floating tablets at 208° C. The above results confirm that there was no drug excipient interaction.

Table.7 Flow Properties of Beclomethasone Dipropionate GR Floating tablets (F1 to F9)

Formulation	Angle of repose (ɵ°) ± SD	Bulk density (g/ml)±SD	Tapped density (g/ml) ± SD	Carr's index (%) ± SD	Hausner's ratio Index ± SD
F1	24.15±0.06	0.51±0.03	0.62±0.05	17.74±0.07	1.21±0.06
F2	25.08±0.03	0.47±0.07	0.59±0.04	20.33±0.02	1.25±0.03
F3	23.28±0.12	0.48±0.05	0.59±0.06	18.64±0.02	1.22±0.03
F4	27.21±0.09	0.54±0.02	0.65±0.07	16.92±0.06	1.20±0.07
F5	28.25±0.02	0.52±0.03	0.63±0.03	17.46±0.05	1.21±0.05
F6	29.35±0.03	0.48±0.05	0.60±0.05	20.00±0.01	1.25±0.04
F7	26.75±0.05	0.47±0.04	0.56±0.06	16.07±0.06	1.18±0.08
F8	24.38±0.06	0.53±0.07	0.62±0.04	14.51±0.05	1.16±0.03
F9	25.02±0.08	0.50±0.02	0.58±0.03	13.79±0.08	1.15±0.05

Precompression parameters of beclomethasone dipropionate were determined and the results of them were shown in table. It ensures good flow property of powders. The results have shown acceptable range of flow properties.

Table.8 Physical Characterization of GR Floating tablets of B D (F1 to F9)

Formulation	Hardness(kg/cm^2)	Thickness(mm)	Diameter(mm)	Avg Wt variation (mg)	Friability	Floating Lag time (Sec)	Floating Duration (hrs)
F1	4.5	5±0.13	9	195±0.13	0.45	118	>24
F2	5.3	4±0.74	9	200±0.16	0.48	158	>24
F3	5.0	5±0.76	9	200±0.16	0.44	155	>24
F4	4.6	5±0.12	9	205±0.25	0.51	105	>24
F5	4.7	4±0.13	9	200±0.17	0.47	200	>24
F6	4.7	4±0.79	9	197±0.12	0.45	250	>24
F7	4.3	6±0.02	9	200±0.17	0.46	0	>24
F8	4.0	7±0.02	9	200±0.10	0.53	0	>24
F9	4.0	7±0.01	10	200±0.25	0.46	0	>24

Table.9 swelling index data of Beclomethasone Dipropionate Floating tablets

Formulation	Swelling Index ±SD; n=3
F1	5.03±0.12
F2	4.56±0.17
F3	4.12±0.26
F4	3.24±0.32
F5	4.01±0.27
F6	4.00±0.28
F7	4.60±0.23
F8	5.33±0.16
F9	6.20±0.18

The results of swelling index studies of GRF tablets of BD have shown in table. It has shown that by increasing the amount of polymer, swelling index was increased and it was determined for 6 hrs.

***Invitro* drug release studies**

The dissolution studies were performed in USP type II apparatus using 0.1N HCL as a medium, maintained at a temperature of 37^0C for about 10 hours.

Table.10 *Invitro* Dissolution Data for Formulation F1 to F9 using HPMCK4M

Formulation	Cumulative %drug release				
	1 hr	3hr	6hr	10hr	12hr
F1	10.26±0.12	21.13±0.51	38.77±0.15	63.17±0.35	68.17±0.73
F2	10.98±0.26	24.47±0.35	40.50±0.24	65.61±0.56	68.72±0.59
F3	11.79±0.38	23.75±0.42	45.46±0.32	64.82±0.71	69.62±0.92
F4	13.5±0.56	25.35±0.85	48.00±0.62	69.04±0.46	70.72±0.49
F5	12.6±0.84	24.64±0.75	46.35±0.43	65.45±0.69	73.22±0.72
F6	14.4±0.65	26.40±0.49	52.15±0.61	71.50±0.73	75.77±0.37
F7	15.21±0.72	27.00±0.94	49.73±0.70	73.52±0.82	76.59±0.64
F8	16.02±0.59	28.72±0.45	51.57±0.86	75.44±0.19	79.12±0.53
F9	16.83±0.28	27.82±0.61	56.40±0.53	76.58±0.25	80.84±0.09

Invitro drug release study for all the nine formulations was carried out for 12hrs and tabulated shown in table. Formulation F9 met the desired drug release profile in 12 hr therefore, considered the best formulation among all the formulations.

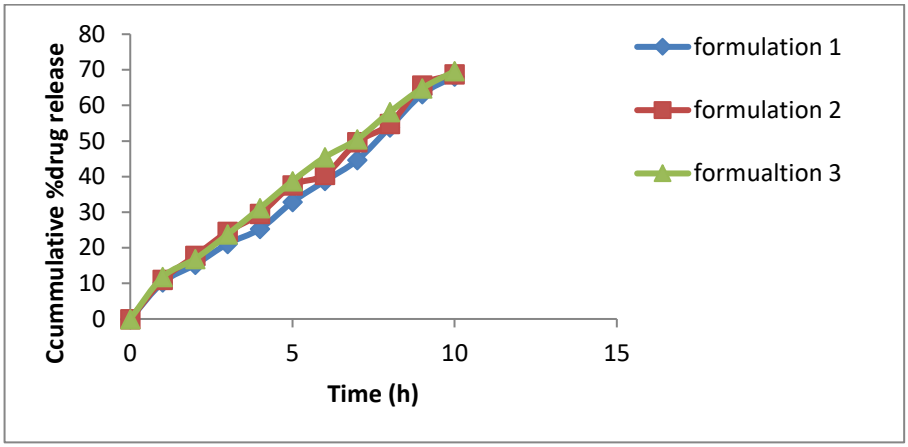

Figure.6 *Invitro* release of Beclomethasone dipropionate by using effervescent method

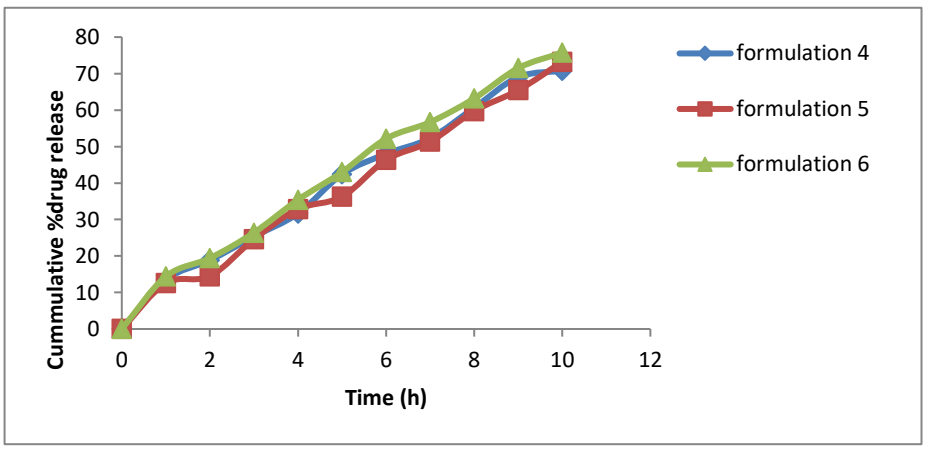

Figure.7 *Invitro* release of Beclomethasone dipropionate by using Non-effervescent method

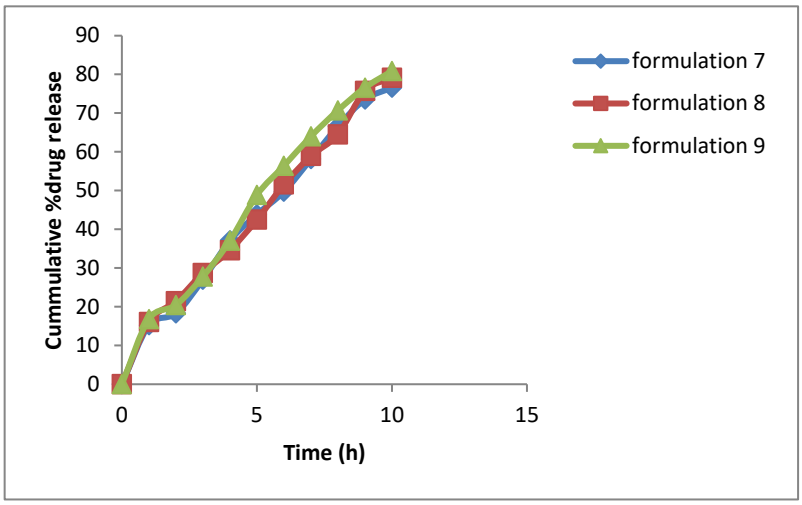

Figure.8 *Invitro* release of Beclomethasone dipropionate by using Sublimation method

Table. 12 Kinetic analysis of dissolution data for formulation 9

ZERO ORDER		HIGUCHI MODEL		PEPPA MODEL		FIRST ORDER	
Time (Hrs)	Cumulative % Drug Release	Sq.Root of Time	Cumulative% Drug Release	Log Time	Log % of Drug Release	Time (Hrs)	Log of %drug remaining
0	0	0	0	0	0	0	0
1	16.83	1.00	16.83	0.00	1.22	1	1.91
2	20.44	1.41	20.44	0.30	1.33	2	1.90
3	27.82	1.73	27.82	0.48	1.44	3	1.85
4	37.04	2.00	37.04	0.60	1.56	4	1.79
5	48.87	2.24	48.87	0.70	1.68	5	1.70
6	56.40	2.45	56.40	0.78	1.75	6	1.63
7	64.00	2.65	64.00	0.85	1.80	7	1.55
8	70.70	2.83	70.70	0.90	1.84	8	1.46
9	76.58	3.00	76.58	0.95	1.88	9	1.36
10	80.84	3.16	80.84	1.00	1.90	10	1.28

Table.13 Correlation coefficient (R2) and release exponent (n) values for different kinetic models of Formulation F9

Model name	R^2 value	Slope
Zero order model	0.986	8.051
First order model	0.980	-0.073
Higuchi's model	0.975	32.67
Korsmeyer-peppas model	0.972	0.788

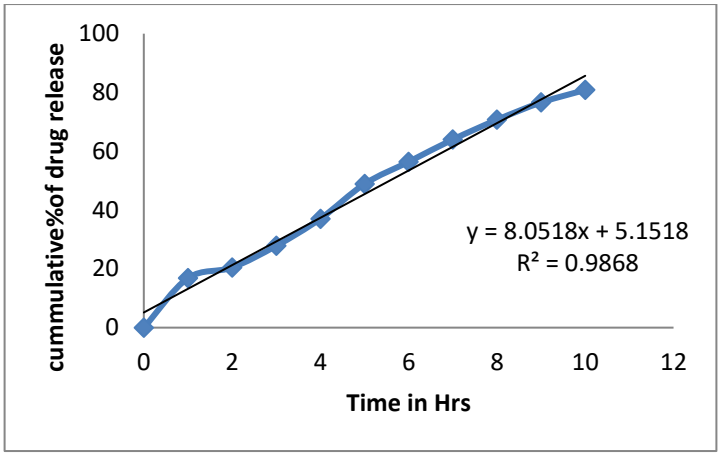

Figure.9 Zero order kinetics of Formulation F9

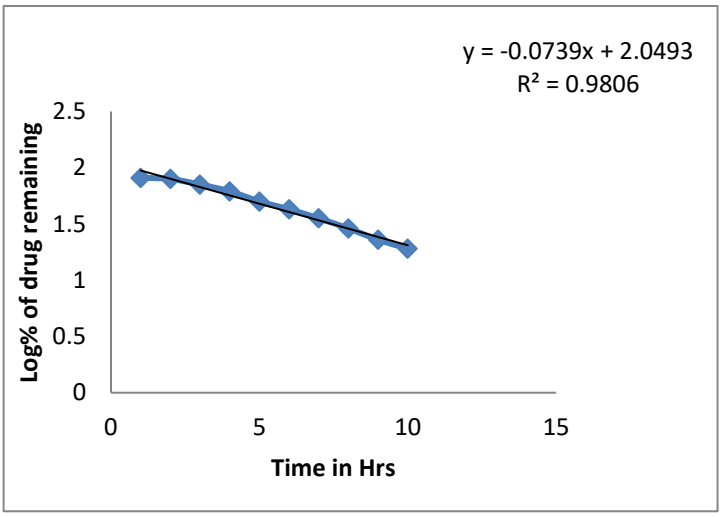

Figure.10 First order kinetics of Formulation F9

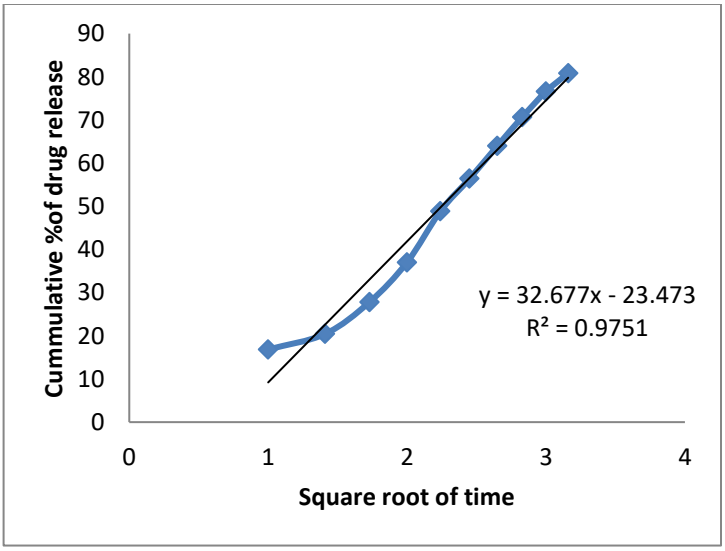

Figure.11 Higuchi model of Formulation F9

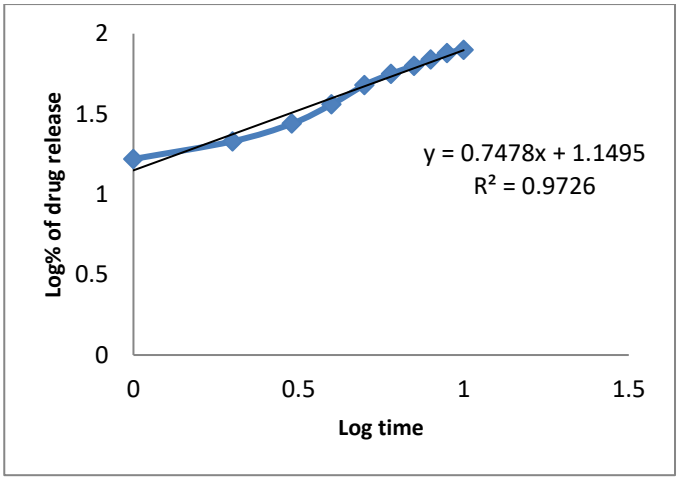

Figure.12 Peppa's model of Formulation F9

Correlation coefficient (R2) and release exponent (n) values for different kinetic models were shown in above table. The n value from the Korsmeyer-peppas model for GRF tablets of BD tablets is 0.747, which is less than 0.89, which shows Anomalous transport of diffusion.

CONCLUSION

The formulations of Gastro retentive floating tablets of Beclomethasone Dipropionate from F1 to F9 with HPMC K4M polymer in different ratios using three different methods such as effervescent, non-effervescent method, and sublimation method were prepared. The formulation F9 prepared has shown 73% of drug release in 12hrs which uses camphor as sublimation material. These tablets has no lag time and floated for over >24hrs.The tablets prepared from F9 formulation retained the drug release up to desired time period due to the presence of pores and polymers such as HPMCK4M and MCC as both the polymers are swellable substances. The drug release kinetics, FTIR and DSC studies of F9 formulation indicated that in the tablets the drug was stable.

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Received:02.08.18, Accepted: 05.09.18, Published:01.10.2018

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