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DEVELOPMENT OF HIGHLY POROUS GASTRORETENTIVE DIPYRIDAMOLE TABLETS USING A SUBLIMATION METHOD

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Abstract:
The present investigation is aimed to formulate floating gastroretentive tablets containing Dipyridamole tabletsusing a sublimation material. The effect of the amount of HPMC K100M on swelling and eroding of the tablets was determined. The water-uptake and erosion behavior of the gastroretentive tablets were highly dependent on the amount of HPMC K100M The water-uptake increased with increasing HPMC K100M concentration in the tablet matrix. The weight loss from tablets decreased with increasing amounts of HPMC K100M. Camphor was used as the sublimation material to prepare gastroretentive tablets that are low-density and easily floatable.Floating properties of tablets and tablet density were affected by the sublimation of camphor. Prepared floating gastroretentive tablets floated for over 24 hrs and had no floating lag time. However, as the amount of camphor in the tablet matrix increased, the crushing strength of the tablet decreased after sublimation. The release profiles of the drug from the gastroretentive tablets were not affected by tablet density or porosity. From the Formulation, Kinetic, FTIR and DSC Studies indicated that the drug was stable in the tablets. HPMC K100M can be used as a rate controlling polymer by appropriate selection in different ratios. The release of the drug from a matrix tablet was highly dependent on the polymer concentrations.

Key words: *Gastroretentive Dipyridamole tablets floating tablets,Sublimation method.*

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INTRODUCTION:

From many decades, various drug delivery systems have been commonly used for drug administration through oral route have been known to provide a prompt release of the drug. Therefore, to achieve as well as to maintain the drug concentration within the therapeutic effective range needed for treatment, it is often necessary to take drugs several times a day. This results in a significant fluctuation in the level of drug in the blood plasma as well as dose dumping may occur [1-2].

Floating drug delivery systems are aimed to retain the drug in the stomach and are useful for drugs that are poorly soluble or unstable in the gastrointestinal fluids. The underlying principle is very simple, i.e., to make the dosage form less dense than the gastric fluids, so that it can float on them. The density of the system can be reduced by incorporating a number of low density fillers into the systems such as hydroxyl cellulose, lactates or microcrystalline cellulose. However, this system is not ideal because its performance is highly dependent on the presence of food and fluid in the stomach [3]. The basic idea behind the development of such a system was to maintain a constant level of drug in the blood plasma inspire of the fact that the drug does not undergoes disintegration [4].

The drug usually keeps floating in the gastric fluid and slowly dissolves at a pre-determined rate to release the drug from the dosage form and maintain constant drug levels in the blood The concept of floating tablets is mainly based on the matrix type drug delivery system such that the drug remains embedded in the matrix which after coming in contact with the gastric fluid swells up and the slow erosion of the drug without disintegration of the tablet takes place [5].

Sometimes for generating a floating system we even need to add some effervescent or gas generating agent which will also ultimately reduce the density of the system and serve the goal of achieving a floating system [6].

These systems have a particular advantage that they can be retained in the stomach and assist in improving the oral sustained delivery of drugs that have an absorption window in a particular region of the gastrointestinal tract and continuously release the drug before it reaches the absorption window, thus ensuring optimal bioavailability [7-8].

Different approaches are currently used to prolong the gastric retention time, such as muco-adhesive, floating, sedimentation, biodegradable superporous hydrogel,and expendable systems [9]. The floating systems are floatable dosage forms that have a long-lasting intragastric buoyancy. This system offers a sustained action to the therapeutic window and better patient compliance [10].

Several technical methods have been used to prepare gastroretentive floating dosage forms such as the hydrodynamically balanced system based on hydrophilic polymers. The surface of the hydrophilic polymer of the formulation becomes swollen and hydrated when it comes in contact with the gastric fluid and then it is floated. Several researchers have investigated gas-generating systems like Effervescent, Non Effervescent and sublimation method [11–13].

The aim of the study is to prepare the gastroretentive floating tablets by using different concentrations of polymer and sublimation method and compressed by direct compression method and analyzing the release of drug from the tablets which depending upon the concentration of polymer HPMC K100M

MATERIALS AND METHODS:

Materials

Dipyridamole procured as a gift sample from Glochem Pvt Ltd. Hyderabad,Telangana,India,HPMC K100M purchased from Merck Specialities Pvt Ltd, Mumbai, India,Camphor purchased from Merck Specialities Pvt Ltd, Mumbai, India,Magnesium Stearate purchased from Merck Specialities Pvt Ltd, Mumbai, India. and all reagents are used in the laboratory are laboratory grades.

Methods

The Dipyridamole along with excipients in different ratios by using sublimation method formulated into floating tablets by Direct Compression method.

Preparation of Gastroretentive tablets of Dipyridamole:

Sublimation method: 150 mg Dipyridamole, Polymer HPMC K100M has taken in different ratios, 30mg of MicroCrystalline Cellulose, 20mg of magnesium stearate as lubricant, and 100mg camphor was mixed with mixture, blend and Weighed for each tablet fed manually into the die of an instrumented single punch tableting machine and directly compressed to make one tablet. The hardness was kept constant (4- 5 N) and was measured with a hardness tester (Monsanto hardness tester). The diameter and thickness of prepared tablets were maintained between 4mm and 5mm. The tablets were sublimated in 60°C Hot air oven, and the weight of the tablets was measured at regular time intervals. Tablets with a final weight equal to the theoretical weight after complete sublimation (Table1) were selected for further experiments. In this study, camphor was completely sublimated within 24 hrs.

Table 1: Formulation Chart

Method	SUBLIMATION METHOD						
Formulations	F1	F2	F3	F4	F5	F6	F7
Concentrations	**1:0.5**	**1:0.75**	**1:1**	**1:1.5**	**1:2**	**1:2.5**	**1:3**
Dipyridamole	150mg	150mg	150mg	150mg	150mg	150mg	150mg
Hydroxy Propyl Methyl Cellulose (K100M)	75mg	100mg	150mg	225mg	300mg	375mg	450mg
MicroCrystalline Cellulose	30mg	30mg	30mg	30mg	30mg	30mg	30mg
Magnesium Stearate	20mg	20mg	20mg	20mg	20mg	20mg	20mg
Camphor	100mg	100mg	100mg	100mg	100mg	100mg	100mg
Before Sublimation	375mg	400mg	450mg	525mg	600mg	675mg	750mg
After Sublimation	275mg	300mg	350mg	425mg	500mg	575mg	650mg

Dissolution study:
The release Dipyridamole of from the GR tablets was studied using the USP dissolution apparatus II (Rotating paddle).The test for buoyancy and in vitro drug release studies are usually carried out in simulated gastric and intestinal fluids maintained at 37±0.5 ºC. In practice, floating time is determined by using the USP dissolution apparatus containing 900ml of 0.1 HCl as a testing medium maintained at 37±0.5 ºC. The rotation speed was 50rpm.The time required to float the dosage form is noted as floating time.5ml Sample was withdrawn periodically from the dissolution medium, replenished with the same volume of fresh medium each time intervals of 1 to 12hrs and the samples are analyzed for their drug contents after an appropriate dilution with 0.1 N Hydrochloric acid by using UV/Visible spectroscopy. The solution was scanned in the range of 200 – 400. at λ_{max}244nm

Pre compression parameters
Bulk density:
It is a ratio of mass of powder to bulk volume. The bulk density depends on particle size distribution, shape and the cohesiveness of particles.

Bulk density = M/Vo
Where,M = mass of the powder, Vo = bulk volume of the powder

Tapped density: 10gm of powder was introduced into a clean, dry 100 ml measuring cylinder. The cylinder was then tapped 100 times from a constant height and the tapped volume was read. It is expressed in gm/ml and is given by

Tapped density = M/Vt
Where,M = mass of the powder, Vt = final tapping volume of the powder

Compressibility index (Carr's index):
Compressibility index is used as an important parameter to determine the flow behavior of the powder. It is indirectly related to the relative flow property rate, cohesiveness and particle size. It is Simple, fast and popular method for predicting flow characteristics. Carr's index can be represented.

$$\text{Carr's index (\%)} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} * 100$$

Hausner's ratio
It is the ratio of tapped density to bulk density. It is given by

Hausner ratio = Tapped density / Bulk density

Angle of Repose
It is defined as the maximum angle possible between the surface of the pile of the powder and the horizontal plane. Fixed funnel method was used. A funnel was fixed to its tip at a given height 'h, above a flat horizontal surface to which a graph paper was placed. The powder was carefully poured through a funnel till the apex of the conical pile just touches the tip of the funnel. The angle of repose was then calculated using the following equation

Angle of repose (θ)= tan-1(h/r)
Where,

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

Post compression parameters

Tablet density

Tablet density is an important parameter for floating tablets. The tablet would float only when its density is less than that of gastric fluid (1.004). The density is determined using following relationship.

$$V = r2\ h\ d = m/v$$

Where,**v** = volume of tablet (cc), **r** = radius of tablet (cm)**h** = crown thickness of tablet (g/cc) and **m**= mass of the tablet

Weight variation

To study weight variation, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight

Hardness:

Hardness or tablet crushing strength (fc) (the force required to break a tablet in a diametric compression) was measured using Monsanto tablet hardness tester . It is expressed in kg/cm2.

Thickness:

The thickness of the tablets was measured using vernier caliper. It is expressed in mm.

Friability (F):

Friability of the tablet determined using Roche friabilator. This device subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping a tablet at I height of 6 inches in each revolution. Preweighted sample of tablets was placed in the friabilator and were subjected to the 100 revolutions. Tablets were de dusted using a soft muslin cloth and reweighed. The friability (F) is given by the formula.

$$F = W_{initial} - W_{final} / W_{initial} \times 100$$

Swelling Index or Water-Uptake Studies

The individual tablets were weighted accurately and kept in 50 ml of water. Tablets were taken out carefully after 60 minutes, blotted with filter paper to remove the water present on the surface and weighed accurately. Percentage swelling (swelling index) was calculated by using the formula:

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

Floating Lag Time

The floating abilities of single tablets were determined in 500 ml pre warmed 0.1 N HCl, and shaken at 70 rpm, 37 ± 0.2°C for 24 hrs, using a shaker apparatus. The floating lag time (time at which tablets start floating) and duration were measured by visual observation.The time taken for dosage form to emerge on surface of medium called floating Lag Time (FLT) or total duration of time (TFT).

Preformulation studies

Preparation of Buffer Solution

Before performing the test for floating Tablets, standard curve of Dipyridamole 0.1N HCl was constructed.

Preparation of 0.1N HCl

A 8.65 ml of Conc. HCl was placed in a 1000 ml volumetric flask and the volume was made up with water and the pH was adjusted to 1.2.

Preparation of Standard Solution Dipyridamole:

Accurately weighed 100mg of Dipyridamole was placed in a 100ml volumetric flask and 50ml of 0.1 N HCl was added to dissolve the drug. The volume was made up to 100ml HCl to give 1000 µg/ml of solution (stock solution -I).

A 10ml aliquot from stock solution -I was taken and diluted to 100ml within a volumetric flask to get 100µg/ml (stock solution -II)

Determination of absorption maxima (λ_{max}) for Dipyridamole:

A 1ml aliquot of standard solution standard solution stock solution-II was diluted to 10ml to give 10 µg/ml standard solutions of Dipyridamole 0.1 N HCl. This solution was scanned on a UV-Visible spectrophotometer against the respective media blank. An absorption maximum (λ_{max}) of 244nm was obtained for all solutions and was selected to prepare standard curve.

Preparation of Standard curve of Dipyridamole:

Aliquotes of 5, 10, 15, 20 and 25 µg/ml of Dipyridamole standard solution of 100 µg/ml (stock solution-II) was taken and diluted to 10ml to obtain concentrations from 0.1 to 1µg/ml with 0.1 N HCl. The absorbances of solutions were determined at 244nm against respective media solutions as blank and a standard curve was plotted.

RESULTS AND DISCUSSION:

Table 2: Calibration curve values

S.No	Conc µg/l	Absorbance
1	0	0
2	0.1	0.044
3	0.2	0.084
4	0.3	0.131
5	0.4	0.175
6	0.5	0.222
7	0.6	0.263
8	0.7	0.310
9	0.8	0.350
10	0.9	0.395
11	1	0.441

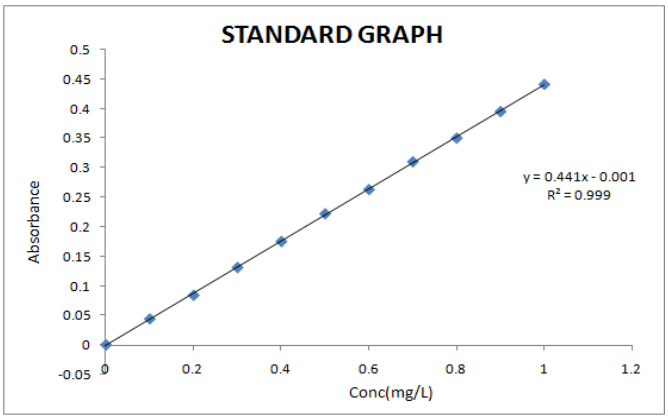

Fig 1: Standard graph of Dipyridamole in 0.1N HCl

Table 3: Pre Compression Parameters:

S.No	Formulation	Angle of repose	Bulk density	Tapped density	Carr's index	Hausners ratio
1	F1	27.91±0.06	0.45±0.03	0.55±0.05	18.18±0.07	1.22±0.06
2	F2	28.23±0.03	0.47±0.07	0.55±0.04	14.54±0.02	1.17±0.03
3	F3	28.34±0.12	0.50±0.05	0.58±0.06	13.79±0.02	1.16±0.03
4	F4	26.71±0.09	0.46±0.02	0.55±0.07	16.36±0.06	1.19±0.07
5	F5	28.32±0.02	0.50±0.03	0.58±0.03	13.79±0.05	1.16±0.05
6	F6	28.23±0.03	0.47±0.05	0.55±0.05	14.54±0.01	1.17±0.04
7	F7	28.24±0.05	0.50±0.04	0.58±0.06	13.79±0.06	1.16±0.08

Table 4: Post Compression Parameters:

Formulation codes	Weight variation(mg)		Hardness(kg/cm2)		Friability (%loss)	Thickness (mm)	Drug content (%)	Floating lag time (min)
	Before Sublimation	After Sublimation	Before Sublimation	After Sublimation				
F1	375±2	275±2	5.1	4.1	0.51	4.8	97.76	0
F2	400±2	300±2	5.2	4.2	0.51	4.9	98.35	0
F3	450±3	350±3	5.2	4.2	0.52	4.9	99.34	0
F4	525±3	425±3	5.3	4.3	0.53	4.9	101.27	0
F5	600±2	500±2	5.3	4.3	0.53	4.7	102.14	0
F6	675±2	575±2	5.4	4.4	0.54	4.5	104.56	0
F7	750±3	650±3	5.5	4.5	0.55	4.4	105.42	0

Dissolution Profiles of different concentration Formulation

Table 5: Percentage of drug release profile

Time (Hrs)	F1	F2	F3	F4	F5	F6	F7
0	0	0	0	0	0	0	0
0.5	10.52±1.50	13.37±1.20	26.62±1.75	15.9±1.26	23.41±1.25	30.41±1.46	4.17±1.02
1	15.31±0.75	28.15±0.89	33.74±1.64	18.97±1.72	28.57±1.75	45.57±0.42	8.11±1.45
1.5	22.34±0.68	41.22±0.86	42.17±0.84	20.91±0.97	32.71±2.71	61.12±0.48	13.13±0.12
2	38.73±1.22	59.05±0.64	51.64±1.26	39.04±0.36	38.88±0.69	74.63±0.46	17.43±0.65
3	57.22±1.44	71.29±1.23	63.21±0.92	46.16±2.01	55.7±0.44	84.52±1.48	26.28±1.45
4	65.29±0.69	82.38±1.44	71.4±0.35	54.29±0.79	72.48±0.25	99.11±1.06	35.34±1.79
5	86.03±0.98	96.82±1.28	79.32±0.46	61.82±0.45	84.41±1.74		47.66±1.34
6	95.07±1.10		86.47±1.25	69.27±1.45	99.69±1.26		58.6±0.15
8			98.61±0.24	80.48±1.76			62.47±0.49
10				97.94±2.1			78.32±0.97
12							87.96±0.84

Table 6 : Release kinetics data

FORMULATION	ZERO ORDER		FIRST ORDER		PEPPAS EQUATION		HIGUCHI PLOT
	K_O	r	K_1	r	r	n	R^2
F1	37.58	0.973	0.122	0.028	0.67	1.73	0.923
F2	44.01	0.956	0.158	0.030	0.507	1.75	0.962
F3	25.42	0.905	0.207	0.123	0.47	1.26	0.998
F4	21.07	0.956	0.145	0.098	0.61	1.25	0.975
F5	35.16	0.981	0.377	0.907	0.54	1.54	0.953
F6	52.87	0.906	0.384	0.087	0.40	1.95	0.948
F7	19.96	0.987	0.181	1.851	0.81	1.36	0.998

Release kinetics data Graphs

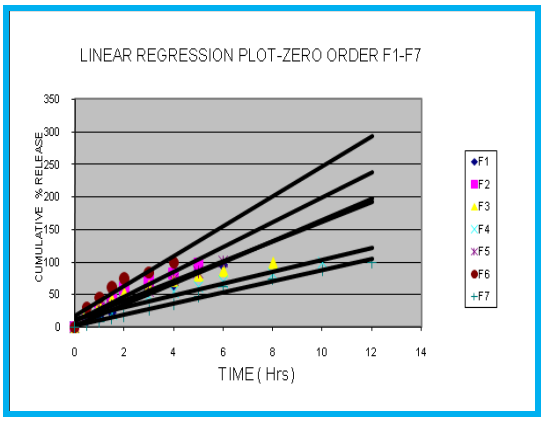

Fig 2 : Zero order release kinetics graph

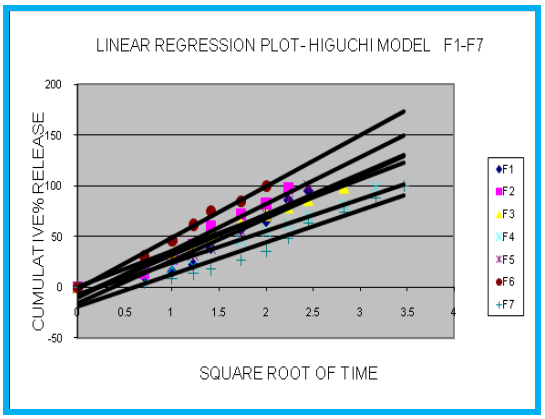

Fig 4: Higuchi release kinetics graph

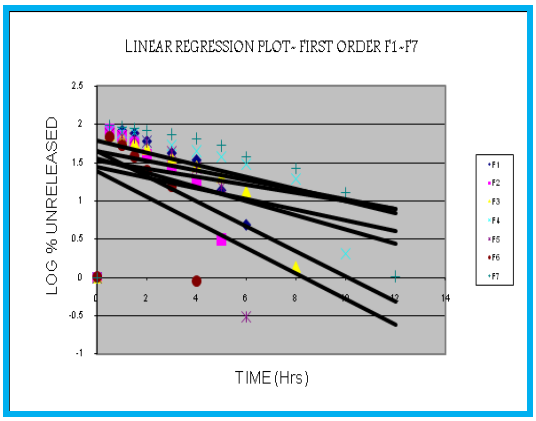

Fig 3: First order release kinetics graph

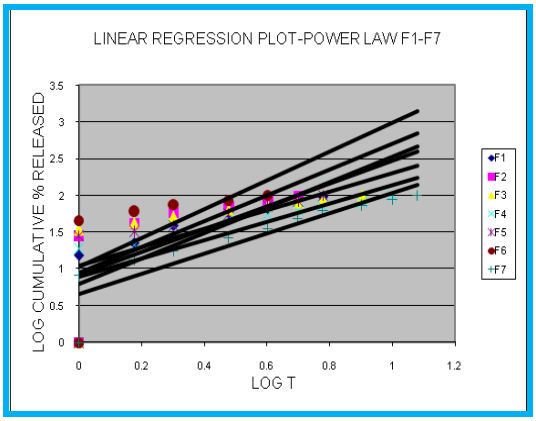

Fig 5: Kars Mayer Peppas graph

Note: By the above studies it is confirmed that the drug release mechanism followed ZERO ORDER KINETICS and HIGUCHI PLOT release mechanisms.

Drug – Exicipent Compatibility Studies

Fourier Transform-Infrared Spectroscopy (FT-IR):

FTIR spectrum of Dipyridamole (Figure 6 and 7) shows a broad peak at 2889cm-^{1}may be due to O-H stretching,1630 cm-^{1} Ar-H stretching and 1362 cm-^{1}C-H stretching, 1342 cm-^{1} may be due to aromatic C=C stretching, 1149 cm-^{1}may be due to C-N, 1060cm-^{1} may be due to C-H bending.962cm-^{1} may be due to – C-O-C group. 947 cm-^{1} may be due to substituted benzene ring. The FTIR spectrum of the best formulation obtained during the from the results, it is clear that, there is no appreciable change in the positions of the characteristic bands of the drug along with the FTIR spectrum of the best formulation derived during the present investigation. Since there is no change in the nature and position of the bands in the formulation, it can be concluded that the drug maintains its identity without going any chemical interaction with the polymer.

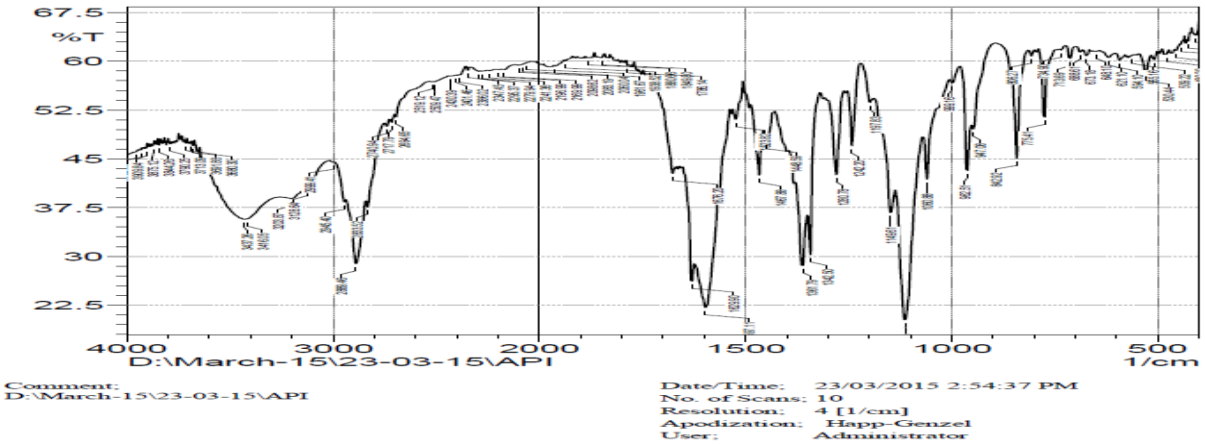

Fig 6: FT-IR Spectrum of Dipyridamole pure drug

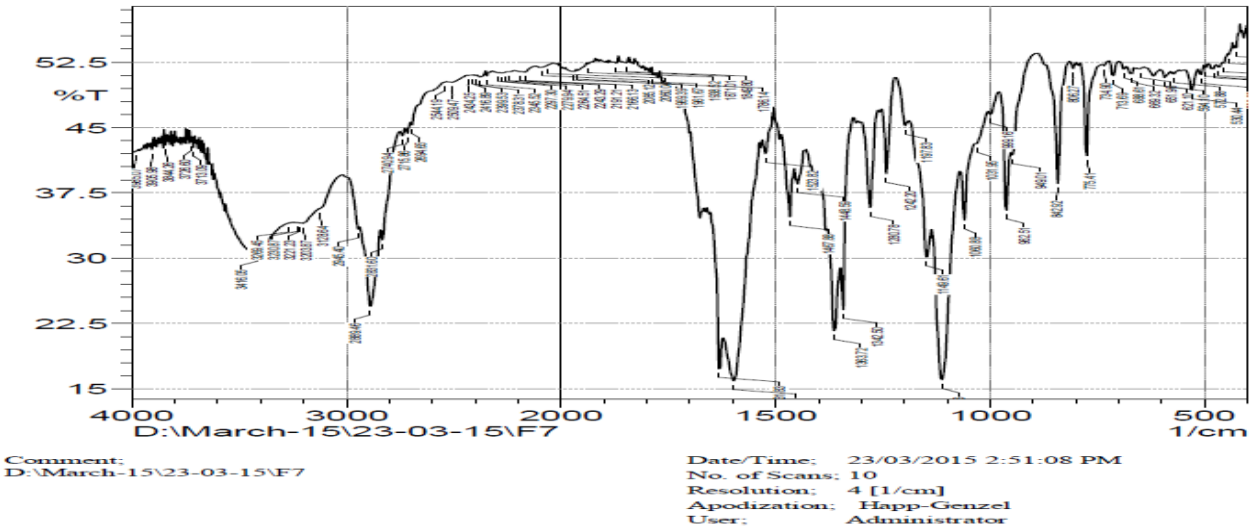

Fig 7: FTIR spectra of Optimized Formulation

Differential Scanning Calorimetry (DSC):
Module: DSC
Data Name: KP
Measurement Date: 03/23/2015
Sample Name: API
Sample Weight: 2.658 mg
Reference Name: Al
Reference Weight: 0.000 mg
Gas: Nitrogen
Pan: Aluminium

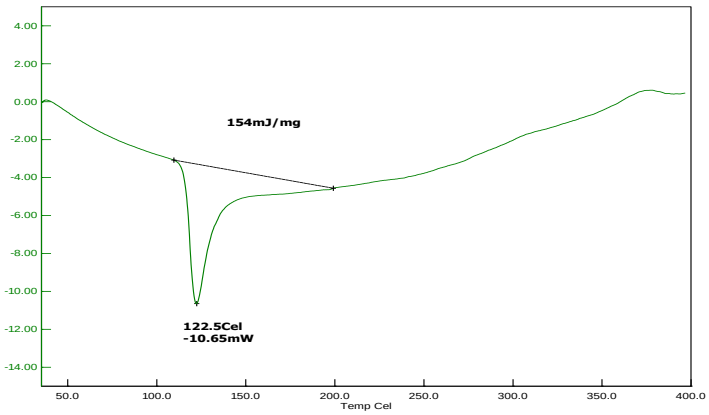

Fig 8: DSC thermograph of API

Module: DSC
Data Name: KP
Measurement Date: 03/23/2015
Sample Name: F7
Sample Weight: 10.183 mg
Reference Name: Al
Reference Weight: 0.000 mg
Gas: Nitrogen
Pan: Aluminium

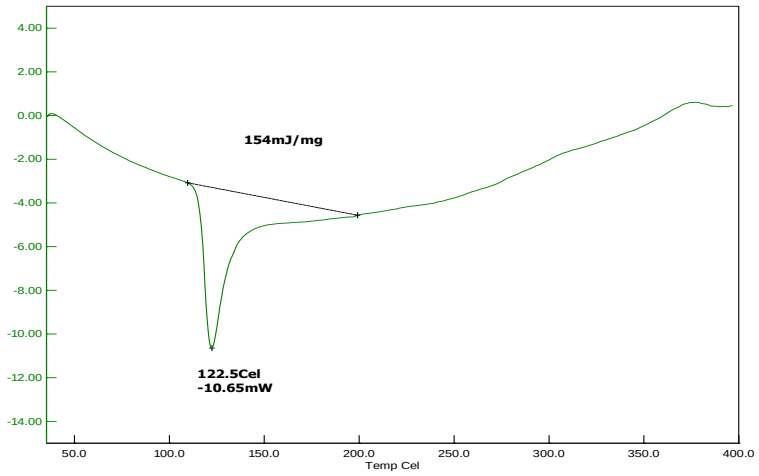

Fig 9: DSC thermograph of Optimized Formulation

DSC study

FigureS 8 and 9 shows the DSC thermographs of before sublimation and After Sublimation tablets. Thermographs obtained from DSC studies, revealed that the melting point of pure drug is 122.5℃ and that of the drug in the frmulation is 122.5℃ as there is no much difference in the melting point of the drug in the thermographs of drug and that of in the formulation. It may be concluded that, the drug is in the same pure state, even in the formulation without interacting with the polymers

Scanning Electron Microscopy (SEM):

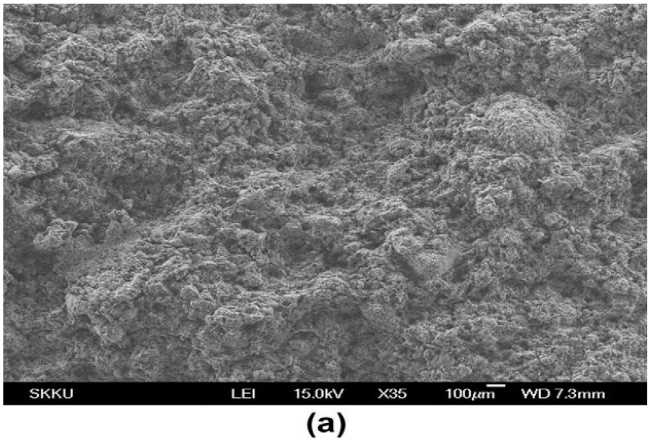

Fig 10: SEM of Tablet before Sublimation

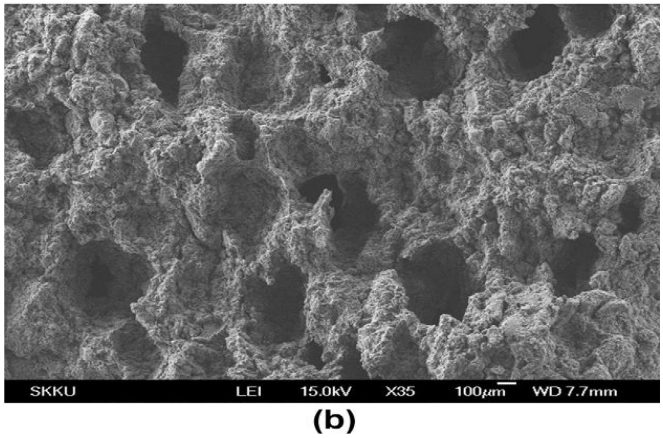

Fig 11: SEM of Tablet after Sublimation

Scanning Electron Microscopy (SEM)study

SEM showed the morphology of a F7 before and after sublimation of camphor. It showed a dense and non-porous structure of the tablet composites before the sublimation. The morphology of the tablet composites after sublimation is highly porous. The pore sizes in the tablet were on the order of several hundred micrometers in diameter. The density and floating property of the tablets were affected by the presence of these pores.

CONCLUSION:

The formulations from F1 to F7 prepared with HPMC K100M polymer in different ratios with Sublimation methods. Among this Sublimation method which having Camphor as sublimation material. The Formulation F7 shows 87.96% of drug release in 12hrs. As Camphor was sublimed, which causes holes and remained in the tablets, giving the tablets a low density and porous structure and increase in tablet thickness after camphor sublimation due to swelling of tablet caused by phase transition of

camphor from solid to gas.The tablets have no lag time and floated over >24hrs.. The formulation F7 could retard the drug release up to desired time period. The tablets containing pores and polymers of HPMC K100M and MCC retard the drug release because both are swellable materials. From the release study it is observed that as increase the concentration of HPMC K100M, the release of drug is decreased. This is possibly due to slower erosion of HPMC K100M due to the increased viscosity of MCC might have the hydrated gel intact thus releasing the drug for 12 hrs. From Formulation, Kinetic, FTIR,DSC studies and SEM Studies indicated that the drug was stable in the tablets. HPMC K100 M can be used as a rate controlling polymer by appropriate selection in different ratios. The release of the drug from a matrix tablet was highly dependent on the polymer concentrations.

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