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Review Article

Formulation and Evaluation of Control Release Clopidogrel Bisulphate Microspheres

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Abstract

This study focuses on the formulation and evaluation of controlled-release microspheres for clopidogrel bisulfate, an antiplatelet agent widely used in the prevention of cardiovascular events. The objective was to develop a sustained-release delivery system that enhances the therapeutic efficacy of clopidogrel while improving patient compliance through reduced dosing frequency. Various biocompatible and biodegradable polymers, including poly (lactic-co-glycolic acid) (PLGA) and HPMC, were utilized to fabricate the microspheres using the solvent evaporation technique. The resulting microspheres were characterized for their physical properties, including particle size, morphology. In vitro drug release studies were conducted to evaluate the release kinetics of clopidogrel bisulfate from the microspheres over an extended period. The results indicated that the formulation achieved a sustained release profile, with a significant reduction in the initial burst release compared to conventional dosage forms. Kinetic modeling of the release data suggested a diffusion-controlled mechanism, indicating that the microspheres can maintain therapeutic drug levels for a prolonged duration.

Keywords: Anti-platelet agent, Microspheres, biocompatible, sustained-release delivery system.

Introduction

Clopidogrel bisulfate is an anti-platelet medication widely used for the prevention of cardiovascular events, particularly in patients with a history of myocardial infarction, stroke, or peripheral arterial disease. It functions by inhibiting platelet aggregation, thereby reducing the risk of thrombus formation. Despite its efficacy, clopidogrel has a relatively short half-life and requires multiple daily doses to maintain therapeutic levels, which can lead to patient non-compliance and fluctuating drug levels in the bloodstream. To address these challenges, the development of controlled-release formulations is of significant interest [1].

Controlled-release drug delivery systems aim to improve the pharmacokinetic and pharmacodynamic profiles of drugs by providing a sustained release of the active pharmaceutical ingredient over an extended period. This approach not only enhances patient compliance by reducing the frequency of dosing but also minimizes the peaks and troughs associated with conventional dosage

forms. In the case of clopidogrel bisulfate, a controlled-release microsphere formulation can ensure a more consistent therapeutic effect, reduce side effects, and improve overall treatment outcomes. Microspheres, as drug delivery vehicles, offer several advantages, including the ability to encapsulate drugs efficiently, enhance bioavailability, and provide targeted delivery. They can be made from various biocompatible and biodegradable polymers, which can further tailor the release profile of the drug. By manipulating the formulation parameters, such as polymer type, drug-polymer ratio, and preparation method, it is possible to design microspheres that achieve the desired release characteristics [2, 3].

Materials and Methods:

Table 1: Chemicals List

S. No.	Chemicals	Brand
1	Drug (Clopidogrel bisulfate)	Sanify Health Care Pvt Ltd Papri Village Mohali Punjab
2	HPMC	Nova Polychem Karol Bagh, New Delhi
3	Ethyl Cellulose	S.D Fine chemicals Ltd, Mumbai, India
4	Carbopol-940	Nova Polychem Karol Bagh, New Delhi
5	Sodium Alginate	Nova Polychem Karol Bagh, New Delhi
6	Poly (lactic-co-glycolic acid):	Nova Polychem Karol Bagh, New Delhi

Preformulation Studies:

Determination of λmax by UV spectroscopy:

Clopidogrel bisulfate UV spectrum was obtained using 0.1 N HCL and a pH 6.8 phosphate buffer. A precise weight of 75mg of Clopidogrel bisulfate was placed into a 200ml volumetric flask, and the volume was adjusted using buffer solution to achieve 100µg/ml. The treatment of this solution was that of stock solution (Stock-I).Using the appropriate buffer solution, I further diluted the stock solution to obtain 10µg/ml. The UV spectrum was then measured at 204nm absorption spectra [4].

Construction of Standard Curve:

Preparation of Stock Solution:

Standard stock solution of Simvastatin was prepared by dissolving 10mg of Clopidogrel bisulfate (Pure drug) in 10ml of 0.1N HCL to obtain 1mg/ml (or) 1000µg/ml. This solution was treated as stock solution (Stock-I). From the stock solution-I withdraw 1ml of solution and further dilute up to 10ml by using 0.1 N HCL to produce the concentration of 100µg/ml (Stock-II).

Preparation of Calibration Curve:

From the stock solution (Stock-II) 0.2, 0.4, 0.6, 0.8, 1.0ml were withdrawn and taken into a separate 10ml volumetric flask. The volume was made up to 10mL by using 0.1 N HCL to obtain the concentration of 2, 4, 6, 8, 10µg/ml respectively. With the aid of UV spectroscopy absorbance of solutions were measured at 204nm to construct the standard curve. This standard curve employed to determine the drug release from the dosage form.

Physical drug Excipients Compatibility Studies:

Fourier transforms infrared spectroscopy:

FTIR study was performed to verify pure drug and polymer interaction. The study of

pure drug Clopidogrel bisulfate and HPMC, Carbopol-940, Poly (lactic-co-glycolic acid) and Ethyl cellulose. The pure drug powder within potassium bromide and pellet was prepared by high pressure to 100kg/cm for 2min. The obtained tablet was investigate in FTIR 8400S, Shimadzu, Japan. KBr was investigated of samples. The process was repeated for determine of drug and components [5].

Melting Point Determination:

Melting point determination was done by using capillary tube (Kumar and Sindhuri 2014).

Solubility:

The spontaneous interaction of two or more substance to form a homogenous molecular dispersion is called as solubility. 75mg of drug was a suspended separately in 75ml of different solvents at room temperature in tightly closed tubes and shaken. The solubility profiles of two drugs in various solvents are shown in the table.2.3 [6].

Table 2: Solubility Profile I.P. 1996

Descriptive term	Parts of solvent required for 1part of solute.
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly Soluble	From 30 to 100
Slightly Soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10, 000
Practically insoluble of Insoluble	Greater than or equal to 10,000

Micrometry study of Powder:

Bulk density and tapped density:

Bulk density is calculated by adding a know mass powder to a cylinder. The density is calculated as mass. Tapped density in this method firstly we have to weigh the known powder and then known powder transfer in a 10ml mechanically tapping cylinder. The tapping is started until the little further volume change is observed [7].

$$\text{LBD} = \text{Wt powder/Vol powder} \quad \ldots\ldots. \quad (1)$$

$$\text{TBD} = \text{Powder wt/Tapped vol powder} \quad \ldots\ldots.. \quad (2)$$

Carr's index:

The powder can be determined by differentiate LBD & TBD of powder & value at which crowded depressed [7].

Carr's index is deliberate by formula:-

$$\% \text{ Carr's index} = \frac{\text{TBD}-\text{LBD}}{\text{TBD}} \times 100 \quad \ldots\ldots. \quad (3)$$

Hausner's ratio:

The Hausner's proportion of compose afloat tablets dried power merge were resolve following equation [8].

$$\text{Hausner's ratio} = \frac{\text{TBD}}{\text{LBD}} \quad \ldots\ldots. \quad (4)$$

2.3.4 Angle of repose:

Angle of repose was investigated by using funnel method of following formula [9].

$$\text{Tan } \theta = \frac{H}{R} \quad \ldots\ldots \quad (5)$$

Where,

θ = angle of repose
H = height of the pile
R= radius of the pile base

Preparation of Microspheres Formulation:

Microspheres of Clopidogrel bisulphate were prepared by ionotropic gelation method using Sodium alginate, lactic-co-glycolic acid, HPMC and Carbopol-940. Weighed quantity of drug and polymer were added to 30ml of sodium alginate solution with stirring at about 300rpm. The resultant solution was then added drop wise using 24 gauge syringe to 100ml of Ethyl Cellulose solution under continuous stirring. Stirring was continued for 30 minutes. The obtained microspheres were filtered and washed with purified water and then dried for 6 hours at 40°C [10, 11].

Table 3: Composition of different Clopidogrel bisulphate Microspheres Formulations (%W/V)

Ingredients mg/ml	**Formulation batch**					
	F1	**F2**	**F3**	**F4**	**F5**	**F6**
Clopidogrel bisulfate	75	75	75	75	75	75
HPMC	0.2	0.2	0.4	0.4	0.2	0.2
Ethyl Cellulose	4	6	8	10	4	6
Carbopol-940	0.2	0.4	0.6	0.8	0.2	0.4
Sodium Alginate	2	2.5	2	2.5	2	2.5
Poly (lactic-co-glycolic acid):	1.5	2	1.5	2	1.5	2
Purified water	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S

Evaluation of Formulation:

Percentage yield:

Thoroughly dried microspheres were collected and weighed accurately. The percentage yield was then calculated using formula given below [12]:

$$\text{Percentage yield} = \frac{\text{Practical yield}}{\text{Theoretical yield}}$$

Drug entrapment efficiency:

Drug loaded micro capsules (75mg) were powdered and suspended in0.1 N HCl. Then the contents suspended in the water were kept for sonication for about 20 minutes and shaking using mechanical shaker for about 20mts for the complete extraction of drug from the microcapsules. The resultant solution was filtered through 0.45µm membrane filter. Drug content was determined by UV-visible spectrophotometer at 204nm [13].

The percent entrapment was calculated by using the following formula:

% drug entrapment efficiency = Practical drug content/theoretical drug content

2.5.3 Swelling Index of Microspheres:
For estimating the swelling index, weighed 100mg of microspheres were allowed to swell in 0.1 N HCL for 24 h. The excess surface adhered liquid drops were removed by blotting and swollen microspheres were weighed by using microbalance. The degree of swelling was calculated by following formula [14, 15].
%Swelling index = wg-wo/wo×100 …….. (6)
Where,
Wo= Initial weight of micro-particles
Wg = Weight of swelled micro-particles in the medium after 8h.

Viscosity Measurement:
A viscometer was used to determine the viscosity of all the formulations at room temperature. The torque readings were obtained between 15%–95% of the base scale. The L4 spindle type set at 10 rotations/min was used.

Morphology:

Scanning electron microscopy (SEM):
The SEM analysis of prepared microspheres was performed for morphological studies. The formulations are poured in to circular aluminium stubs using double adhesive tape, and coated with gold in HUS -5 GB vacuum evaporator , and observed in Hitachi S-3000 N SEM at an acceleration voltage of 10Kv and a magnification of 5000X [16].

In vitro Dissolution studies:
In vitro dissolution study was performed using USP dissolution test apparatus-I (basket assembly). The dissolution was performed using 900ml of 0.1 N HCl solution for 1 hr. and after 1 hr. 0.1 N HCl was replace by phosphate buffer solution (pH 6.8) for 11hr. as dissolution media maintained at 37± 0.5°C and 50 rpm. Samples (5ml) were withdrawn at regular intervals and volume was replaced with fresh dissolution medium to maintain sink condition. Samples were filtered through filter paper and assayed spectrophotometrically on UV-visible spectrophotometer at 204nm wave length for 0.1 N HCl (pH 1.2) and at 204nm for phosphate buffer solution (pH 6.8). For each formulation, the release was repeated in triplicate, results are expressed as a mean ±S.D [18, 19].

Kinetic Parameter:

Zero order:
The rate of those zero order reaction does not very with neither increasing nor decreasing reactants concentration. This implies that the speed of reaction is up to the speed constant, (k) of the reaction following equation [20, 21].

$$M = Mo - Kot \quad \ldots\ldots (7)$$

Where,
M= drug amount release.
Mo= total release drug amount.
Kot= rate constant.

First order:

First order is defined as that proceeds at a rate that on linearly on single reactant concentration. It is given by this equation [22, 23].

$$\text{Log } C = \text{Log } Co - Kt/2.303 \quad \ldots\ldots. (8)$$

Where,

C= drug release amt.

Co= total release drug amount.

K= rate constant.

Korsmeyer Peppas model:

The Korsmeyer Peppas model empirical related the function of time for diffusion controlled mechanism; it is given by this equation [24].

$$mt/m\infty = ktn \quad \ldots\ldots.. (9)$$

Where,

mt / M∞ = could be a selection of drug release t

kt = Constant release rate

n = Exponent release

Higuchi model:

The unleash of a drug from the DDS involves dissolution. Higuchi equation has become a kinetic equation [25].

$$Ft = Kht1/2 \quad \ldots\ldots... (10)$$

Where,

Ft = amount release drug

t = time

Kh = constant rate release

Stability Studies:

The microspheres prepared in the present study were filled in the hard gelatin capsules and then filled in HDPE containers and stored at the following conditions like 40°C/75 RH for 3 about months as per ICH guidelines. The samples were characterized for % drug content [26, 27].

Results and Discussion:

Preformulation Study:

Determination of λ max by UV spectroscopy:

Calibration of Clopidogrel bisulfate in 0.1N Hydrochloric acid at 204nm

Table 4: Calibration curve of Clopidogrel bisulfate in 0.1NHCL pH 1.2

S.No	Conc. (µg/ml)	Absorbance
1	0	0.0
2	2	0.161
3	4	0.335
4	6	0.493
5	8	0.661
6	10	0.790

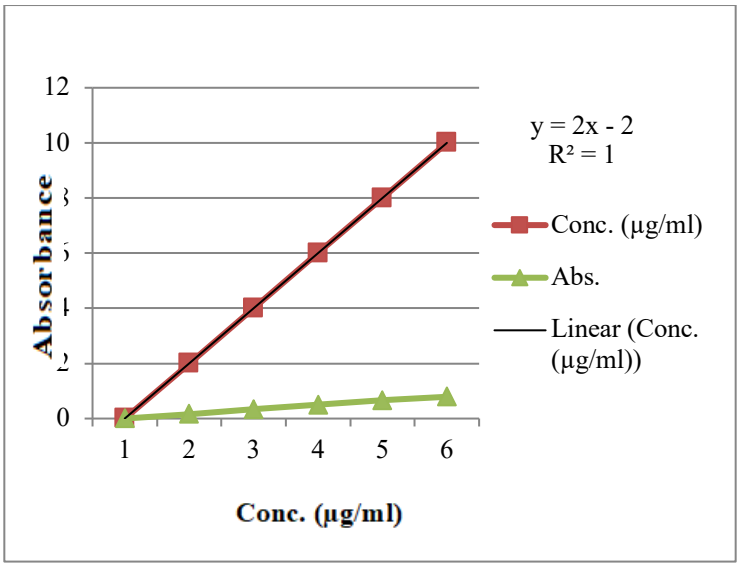

Fig.1: Standard calibration curve of Clopidogrel bisulfate in 0.1N HCl

Calibration of Clopidogrel bisulfate in pH6.8 Phosphate buffer at 204nm:

Table 5: Calibration curve of Clopidogrel bisulfate in 6.8pH phosphate buffer

S.No.	Conc. (µg/ml)	Abs.
1	0	0.000
2	2	0.150
3	4	0.239
4	6	0.367
5	8	0.445
6	10	0.524

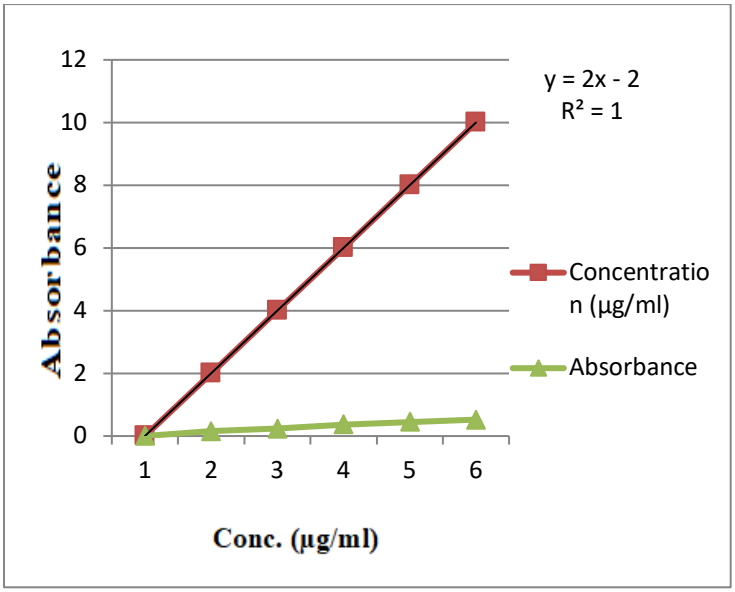

Fig.2: Standard calibration curve of Clopidogrel bisulfate in 6.8pH phosphate buffer

FTIR Study:

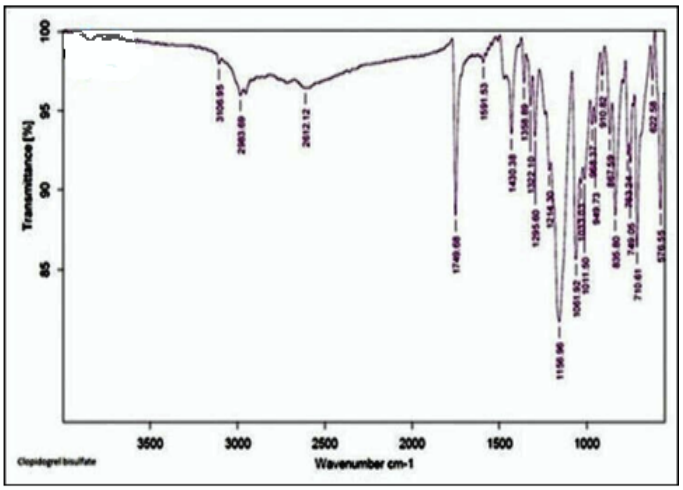

Fig.3: FT-IR spectrum of Pure Clopidogrel bisulfate & Ethyl Cellulose

Table 6: Characterization of peak in FT-IR spectrum of Clopidogrel bisulfate & Ethyl Cellulose

Standard wave number (cm^1)	Observed peaks (cm^{-1})	Functional groups
3550	3510.01	Free OH stretching
2924	2919.11	Methyl C-H symmetric Stretching
2969	2960.22	Methyl C-H asymmetric Stretching
2871	2868.12	Methylene C-H symmetric Stretching
1450	1453.72	C-H bending
1461	1458.43	Methylene C-H symmetric Stretching
1267	1260.65	Lactone C-O-C bending
1225	1224.20	Lactone C-O-C bending
1166	1160.40	Ester C-O-C bending
1072	1070.32	Secondary alcohol C-O Stretching

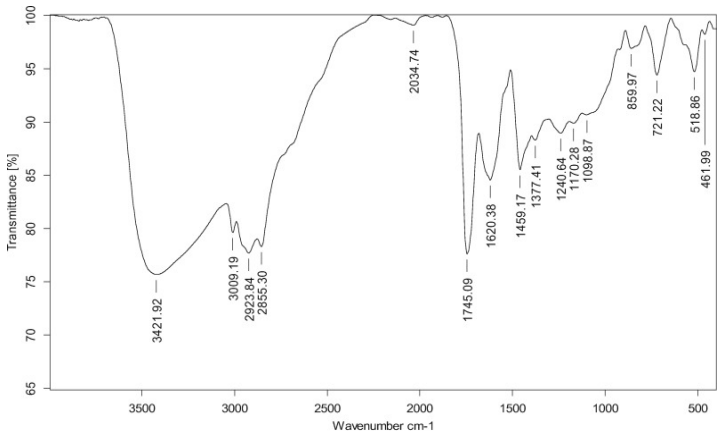

Fig.4: FT-IR spectrum of Poly lactic-co- glycolic acid

Table 7: Characterization of peak in FT-IR spectrum of Poly lactic-co- glycolic acid

Standard wave number (cm^{-1})	Observed peaks (cm^{-1})	Functional Groups
3400-3300	3426.39	N-H Stretching
2885-3010	2915.21	C-H Stretching
1627	1621.12	COO Stretching
1397	1394.23	C=O bending
1415	1403.42	S=O Stretching
1350	1343.59	S=O Stretching
842	938.6	S=O Stretching
586-699	1169.13	C-O Stretching
430	829.17	C-H bending

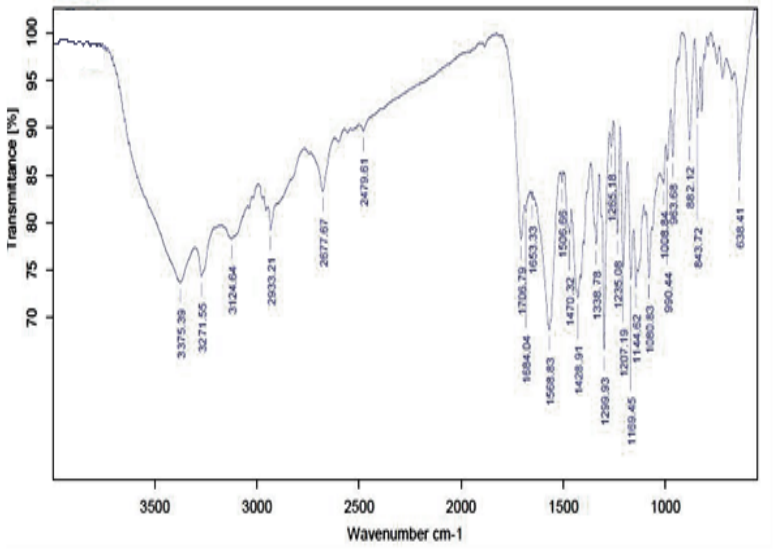

Fig.5: FT-IR spectrum of HPMC

Table 8: Characterization of peak in FT-IR spectrum of HPMC

Standard wave number(cm^{-1})	Observed peaks (cm^{-1})	Functional groups
3550-3200	3349.3	O-H stretching
1626	1660.8	C=C Stretching
1465	1450.12	C-H bending
1372	1346.82	S=O Stretching
1342	1331.54	S=O Stretching
1410	1315.61	S=O Stretching
1124	1126.57	C-O Stretching
1057	1054.12	C-O-C Stretching

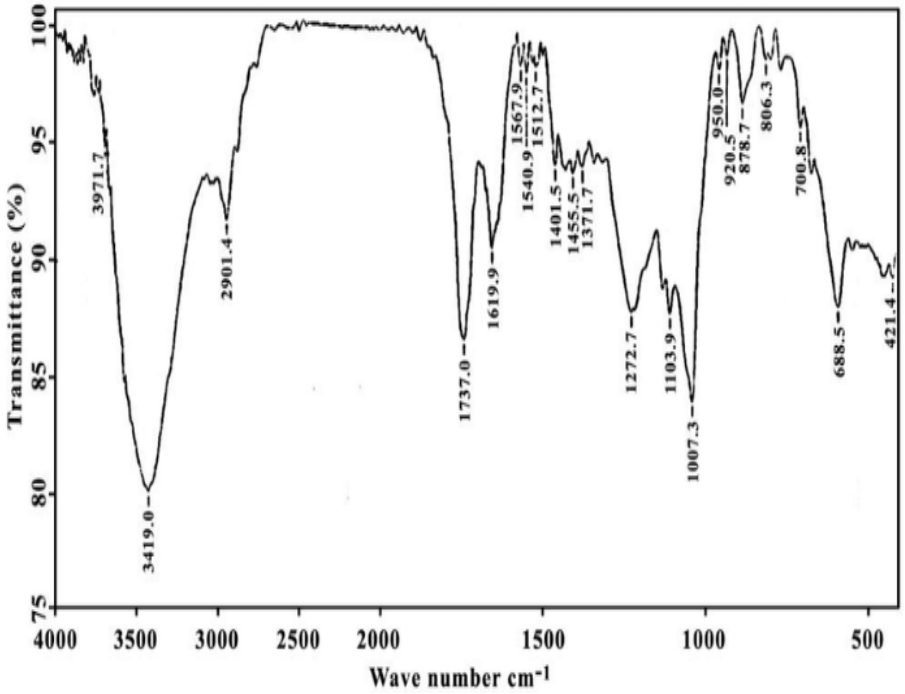

Fig.6: FT-IR spectrum of Carbopol-940 & Sodium alginate

Table 9: Characterization of peak in FT-IR spectrum of Carbopol-940 & Sodium alginate

Standard wave number (cm^{-1})	Observed peaks (cm^{-1})	Functional groups
3550-3200	3430.22	O-H stretching
2925	2919.14	C-H symmetric Stretching
1638	1630.06	C=C Stretching
1417	1410.04	COO symmetric Stretching
1385	1386.06	C-H bending
1275	1270.19	C-O Stretching
1150	1118.20	C-O Stretching
1030	1036.41	C-O-C Stretching
820	828.67	C-H Stretching

There are no discernible peaks beyond the standard peak in the spectra of the medication and excipients mixture, suggesting that the two are compatible and that there is no interaction between them. The drug was found to be stable during the microspheres formulation's creation, as evidenced by the lack of noticeable peak shifting between the IR spectra of the drug and polymer combination and those of the pure drug and individual excipients.

Melting Point:

Table 10: Melting Point Determination

Drug	Melting Point	Normal Range
Clopidogrel bisulfate	199°C	198-200°C

Solubility:

Table 11: Solubility Profile of Clopidogrel bisulfate

S. No	Solvents System	Solubility (mg/ml) at 37±2˚C
1	Distilled H2O	11.3
2	Ethanol	76
3	Chloroform	82
5	CCL4	90
6	Diethyl Ether	26

Evaluation of Powders:

Table 12: Evaluation of Powders for Clopidogrel bisulfate microspheres

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Carr's index (%)	Tapped density (gm/cc)	Hausner's ratio
F1	25.20±0.12	0.56±0.02	26.15±0.9	0.70±0.04	1.45±0.14
F2	22.36±0.04	0.54±0.12	24.36±0.6	0.75±0.06	1.39±0.18
F3	24.86±0.04	0.50±0.05	20.50±1.2	0.65±0.06	1.26±0.23
F4	23.25±0.09	0.62±0.08	30.68±0.8	0.60±0.05	1.08±0.20
F5	26.54±0.10	0.60±0.09	26.09±0.7	0.59±0.02	1.28±0.18
F6	27.64±0.06	0.58±0.10	31.50±0.8	0.68±0.09	1.35±0.13

Values are expressed as mean ±SD (n=3)

Discussion:

The physical mixtures for matrix tablet were evaluated with respect to Angle of repose was found between 25.20±0.12 to 27.64±0.06 and Carr's index values were found 20.50±1.2 to 31.50±0.8% the powder of all batches excellent to poor flow ability and compressibility. Hausner ratio was found to be 1.08±0.20 to 1.39±0.18. Bulk density ratio 0.56±0.02to 0.58±0.10 and tapped density ratio 0.59±0.02 to 0.68±0.09 for all the batches indicating that possible and poor flow properties.

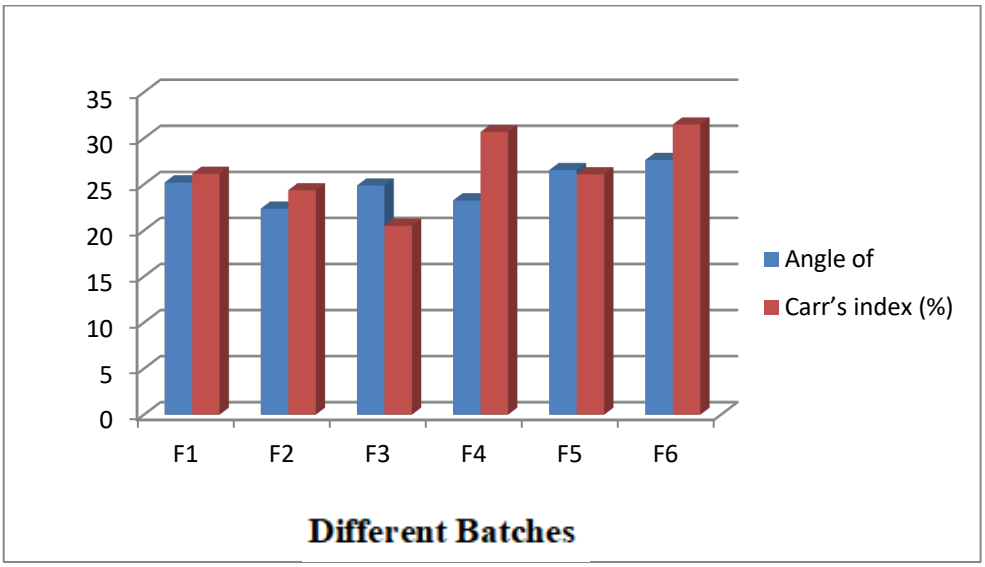

Fig.7: Graphical representation of Carr's index & angle of repose found in different batches of formulation

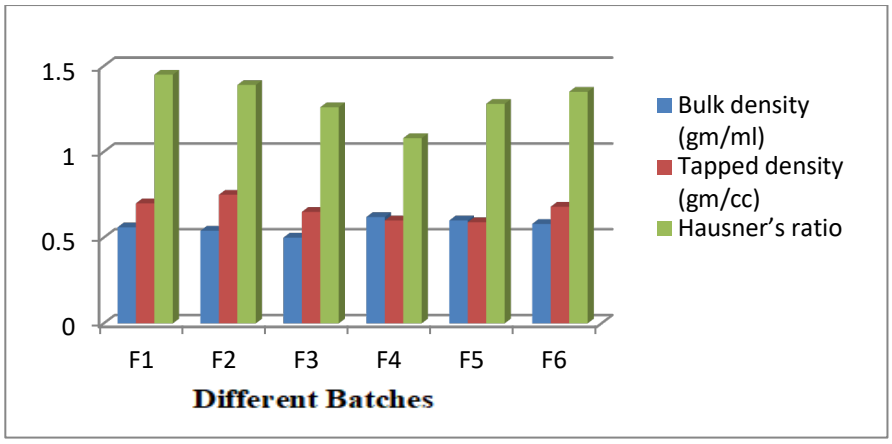

Fig.8: Graphical representation of bulk, tapped density & Hausner's ratio in different batches of formulation

Evaluation of Formulation:

Table 14: Evaluation Parameters

Formulation Code	Percentage yield	Drug entrapment efficiency	Swelling Index of Microspheres	Viscosity (cps)*
F1	94.32±1.19	84.6±0.64	82±0.75	58.5±0.4
F2	92.78±1.23	88.5±0.34	90±0.42	82.2±0.6
F3	96.65±1.53	78.4±0.76	92±0.76	92.6±0.1
F4	97.12±1.41	81.2±0.56	89±0.26	102.2±0.4
F5	90.87±1.34	79.9±0.90	94±0.56	108.6±0.1
F6	94.32±1.24	84.7±0.94	96±0.36	112.2±0.3

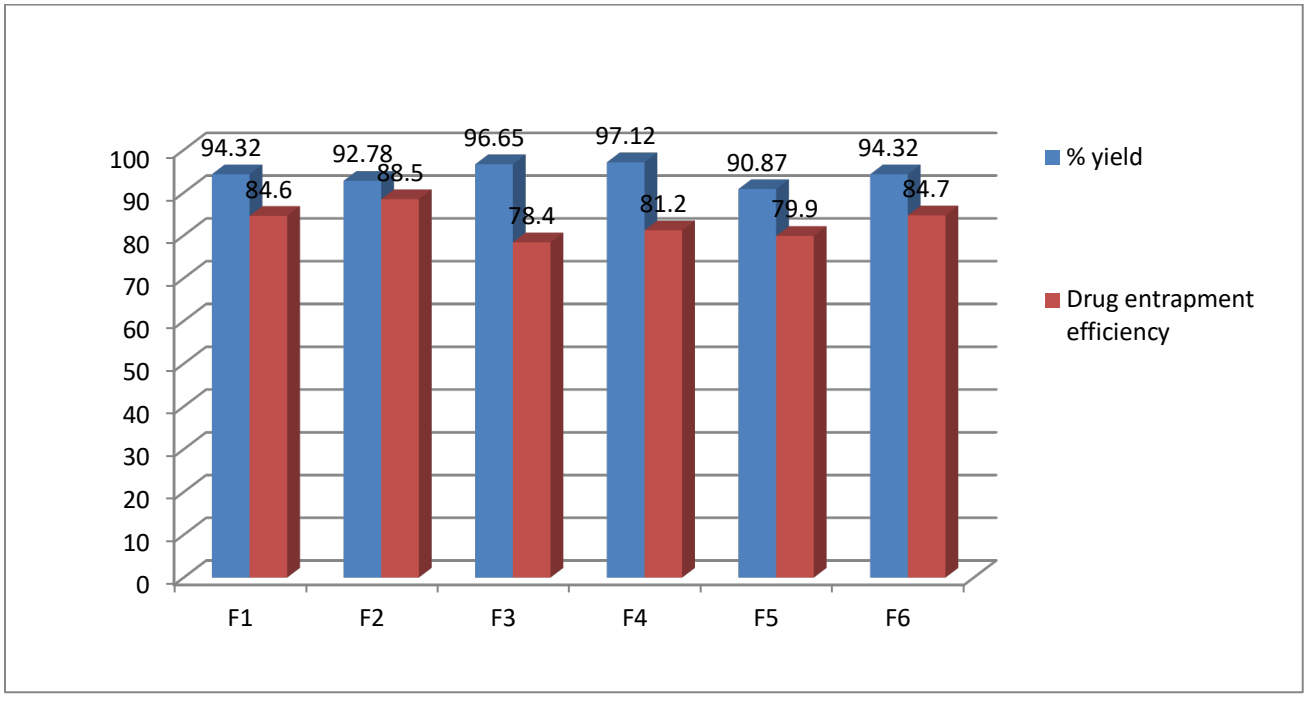

Fig.9: Graphical representation of % Yield & Drug entrapment Efficiency

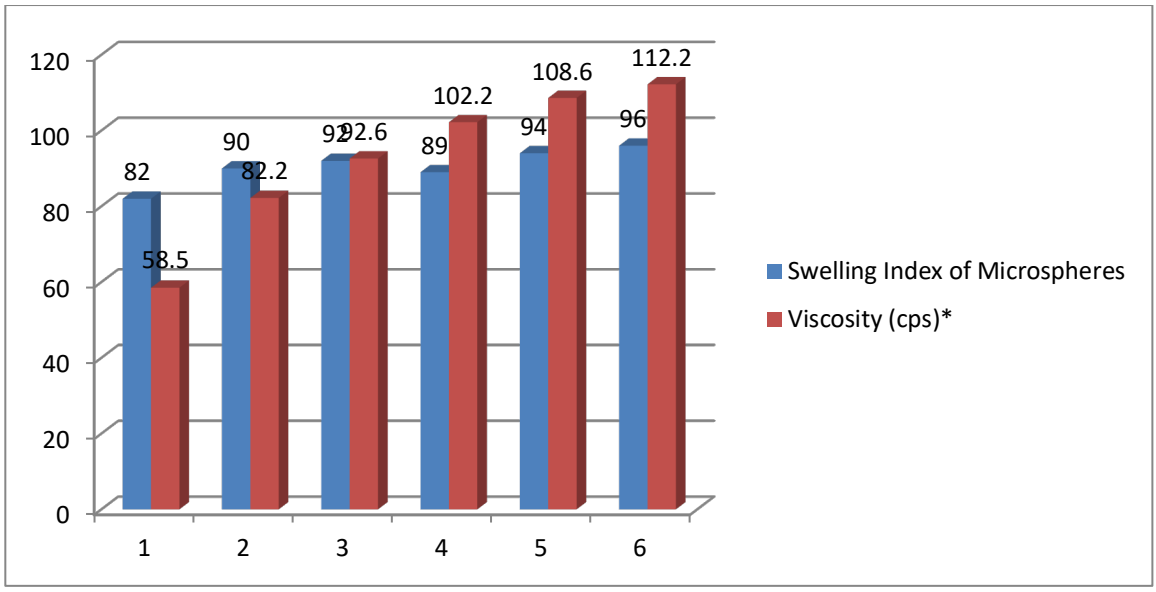

Fig.10: Graphical representation of Swelling index & Viscosity

Scanning Electron Microscopy (SEM):

Microspheres with a narrow size distribution were prepared by modified solvent injection method using Gleceryl Monostearate as a solid lipid. The small and uniform sized microspheres can be prepared by this method without using any sophisticated instruments. The SEM study revealed that most of the microspheres were fairly spherical in shape, the surface of the particle showed a characteristic smoothness, and that the particle size was in the micro-metric range, as depicted in Fig.11.

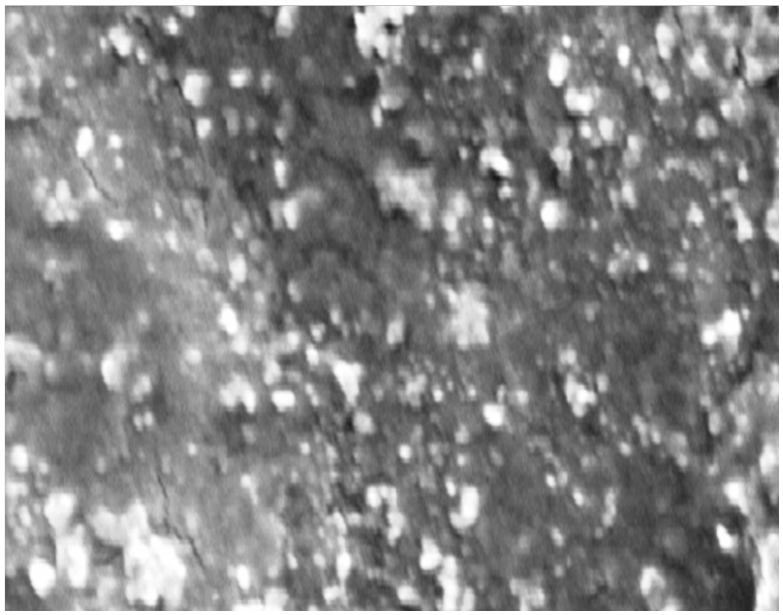

Fig.11: Scanning Electron Microscopy of microspheres

In-vitro drug release study:

Table 15: In-vitro drug release study of Formulation F1 to F6

Time (hr)	% Drug Diffused					
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
1	21.33	24.12	20.54	2 8.90	26.05	26.98
2	35.88	36.78	34.87	35.86	36.90	37.98
3	47.95	48.34	41.85	42.36	44.66	42.42
4	56.74	59.88	58.94	56.90	58.64	59.34
5	68.43	70.65	60.56	64.88	63.78	62.76
6	78.62	79.91	76.14	77.18	79.74	70.56
7	88.84	89.78	86.26	87.78	89.00	80.01
8	93.72	95.70	96.34	95.03	98.92	91.87

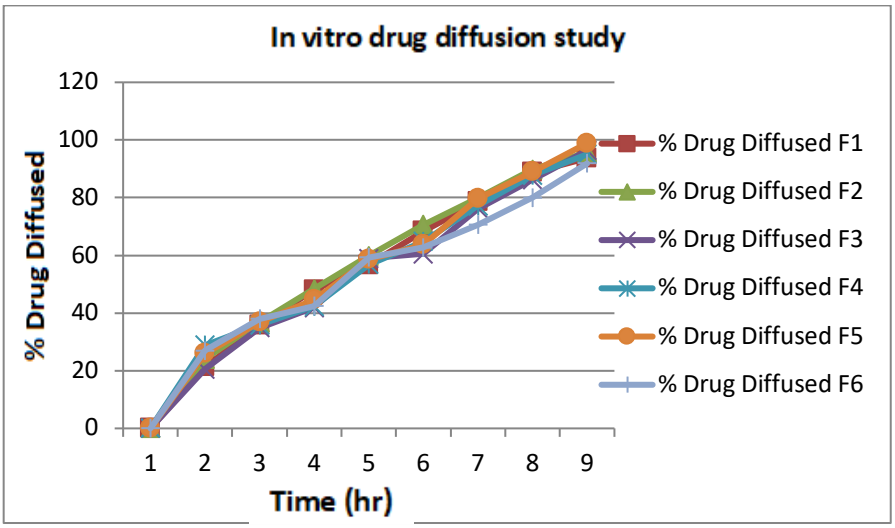

Fig.12: In-vitro drug diffusion study of Formulation F1-F6

Kinetic Parameter:

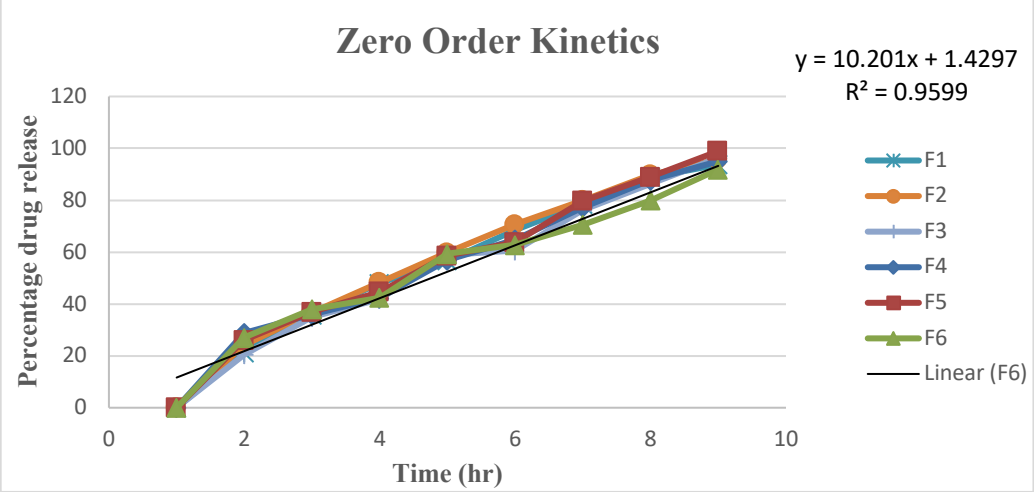

Fig.13: Zero-order release kinetics

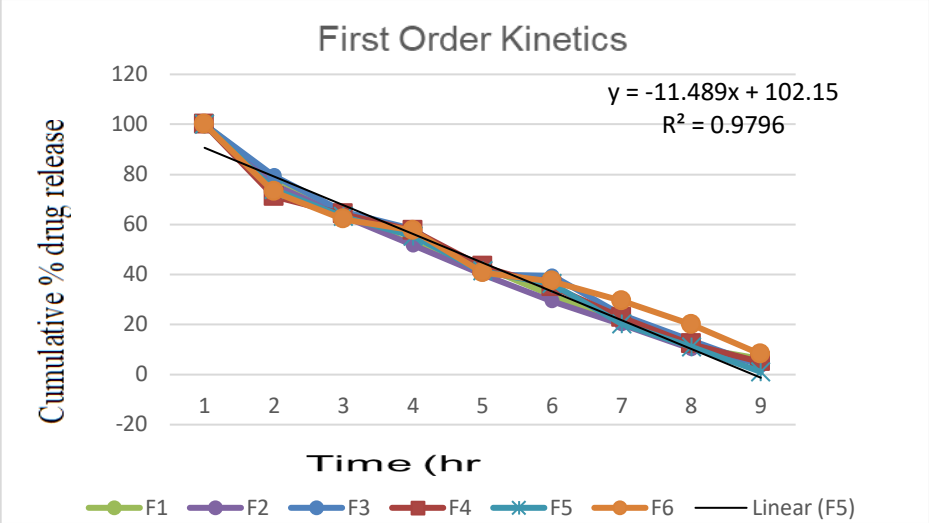

Fig.15: 1st-order release kinetics

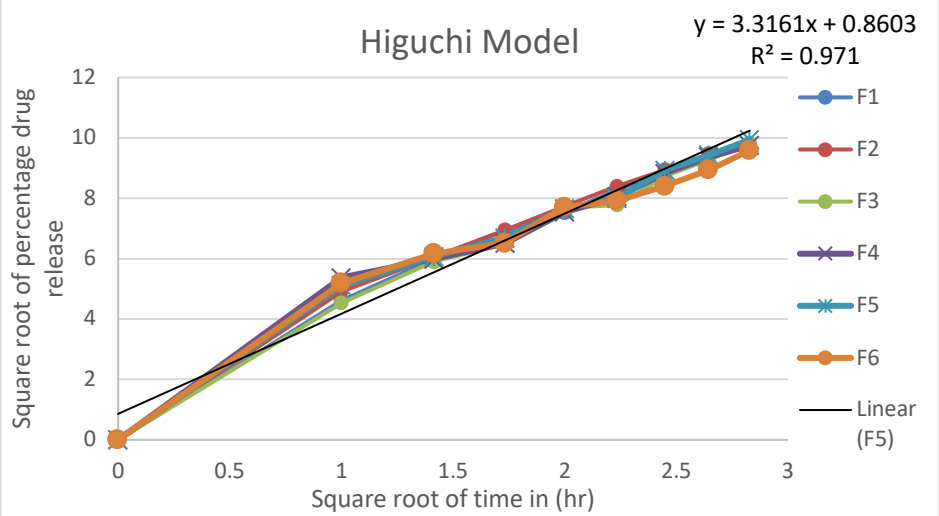

Fig.16: Higuchi models unleash kinetics

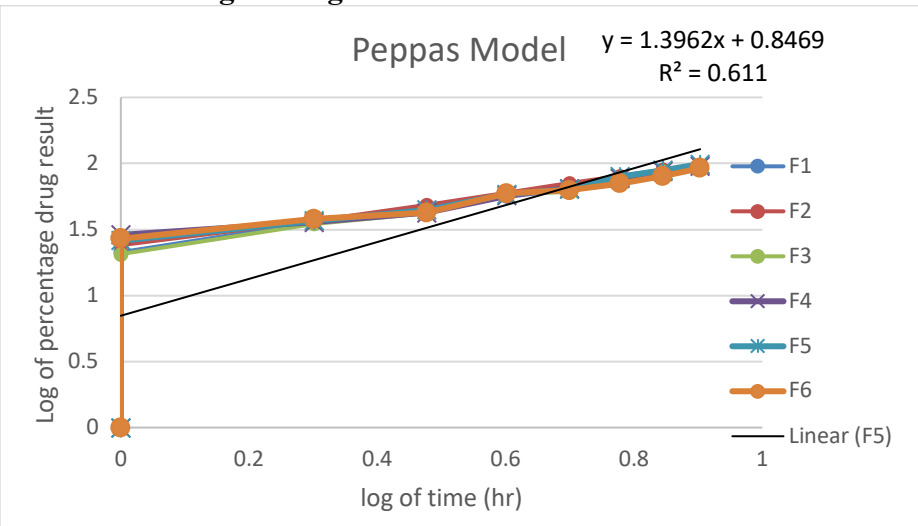

Fig.17: Peppas model release kinetics

Table 16: Release kinetics for all Microspheres formulation

Formulation code	Zero-order	1st-order	Higuchi	Peppas
	r^2	r^2	r^2	r^2
F1	0.978	0.978	0.978	0.642
F2	0.975	0.975	0.973	0.623
F3	0.982	0.981	0.981	0.651
F4	0.973	0.973	0.961	0.590
F5	0.979	0.979	0.971	0.611
F6	0.959	0.979	0.971	0.611

Stability Study:

Table 17: Stability Study best formulation F5

Evaluation Parameters	Initial day	Stability after 1 month	Stability after 2 month	Stability after 3 month
Percentage yield	90.87±1.34	90.87±1.34	90.87±1.34	90.87±1.34
Viscosity (cps)	108.6±0.1	108.2±0.1	108.1±0.1	108.0±0.0
% drug release	98.92	98.78	98.68	98.34

All the prepared Microspheres formulations were found to be unchanged upon the storage for 3 months; no change was developed in their but various changes in viscosity and % drug release.

Conclusion:

Microspheres of Clopidogrel bisulphate were prepared by ionotropic gelation method using Sodium alginate, lactic-co-glycolic acid, HPMC and Carbopol-940. Drug and polymers were compatible with each other as indicated by FT-IR study. Among the different formulations prepared in this study, formulation F5 was shown better results for percentage drug entrapment efficiency (79.9±0.90%), sphericity, and in-vitro drug release (98.92%) up to 8 hours, which contains lactic-co-glycolic acid of 1:3. According to the coefficient of regression, the Higuchi equation, zero order kinetics, and non-Fickian type diffusion provided the best match for the release data. These Control Release micro-particle are thus suitable for oral controlled release of Clopidogrel. The potential of clopidogrel bisulfate microspheres to improve the anti-platelet agent's therapeutic effectiveness and patient compliance was effectively established.

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