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Design and Evaluation of Regioselective Drug Delivery System By Using Dipyridamole Deug As Model

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Abstract: *In the present research work the gastro retentive floating matrix formulation of Dipyridamole by using various hydrophilic polymers. Initially analytical method development was done for the drug molecule. Absorption maxima was determined based on that calibration curve was developed by using different concentrations. Gas generating agent sodium bicarbonate concentration was optimized. Then the formulation was developed by using different concentrations of polymers of various natural polymers. The formulation blend was subjected to various preformulation studies, flow properties and all the formulations were found to be good indicating that the powder blend has good flow properties. Among all the formulations the formulations prepared by using Xanthum gum were unable to produce desired drug release, they were unable to retard drug release up to 12 hours. The formulations prepared with HPMC K15 M retarded the drug release up to 12 hours in the concentration of 200 mg (F8).The formulations prepared with Guar gum were also retarded the drug release for more than 12 hours. Hence they were not considered. The optimized formulation dissolution data was subjected to release kinetics, from the release kinetics data it was evident that the formulation F8 followed Zero mechanism of drug release.*

Keywords: *Dipyridamole, Guar gum , Xanthum gum ,HPMC K15 M and Floating tablets.*

I. Introduction

1.1. INTRODUCTION ON FLOATING DRUG DELIVERY SYSTEMS

Buoyant/ Floating Systems: *Floating Drug Delivery Systems* (FDDS) have a bulk density lower than gastric fluids and thus remain buoyant in the stomach for a prolonged period of time, without affecting the gastric emptying rate. While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the system. After the release of the drug, the residual system is emptied from the stomach. This results in an increase in the GRT and a better control of fluctuations in the plasma drug concentrations.

Based on the mechanism of buoyancy, two distinctly different technologies have been utilized in development of FDDS which are:Effervescent System, andNon- Effervescent System.

EFFERVESCENT SYSTEM:-Effervescent systems include use of gas generating agents, carbonates (ex. Sodium bicarbonate) and other organic acid (e.g. citric acid and tartaric acid) present in the formulation to produce carbon dioxide (CO_2) gas, thus reducing the density of the system and making it float on the gastric fluid. An alternative is the incorporation of matrix containing portion of liquid, which produce gas that evaporates at body temperature.

These effervescent systems further classified into two types.

- Gas Generating systems
- Volatile Liquid/Vacuum Containing Systems.

NON-EFFERVESCENT SYSTEMS: The Non-effervescent FDDS based on mechanism of swelling of polymer or bioadhesion to mucosal layer in GI tract. The most commonly used excipients in non-effervescent FDDS are gel forming or highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming material such as Polycarbonate, Polyacrylate, Polymethacrylate, polystyrene as well as bioadhesive polymer such as Chitosan and Carbopol. The various types of this system are as:

Single Layer Floating Tablets: They are formulated by intimate mixing of drug with a gel-forming hydrocolloid, which swells in contact with gastric fluid and maintain bulk density of less than unity.

Bilayer Floating Tablets: A bilayer tablet contain two layer one immediate release layer which release initial dose from system while the another sustained release layer absorbs gastric fluid, forming an impermeable colloidal gel barrier on its surface, and maintain a bulk density of less than unity and thereby it remains buoyant in the stomach.

Alginate Beads: Multi unit floating dosage forms were developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm diameter can be prepared by dropping a sodium alginate solution into aqueous

solution of calcium chloride, causing precipitation of calcium alginate leading to formation of porous system, which can maintain a floating force for over 12 hours.

Hollow Microspheres: Hollow microspheres (micro balloons), loaded with drug in their outer polymer shells were prepared by a novel emulsion-solvent diffusion method. The ethanol: dichloromethane solution of the drug and an enteric acrylic polymer was poured into an agitated aqueous solution of PVA that was thermally controlled at 40^0C. The gas phase generated in dispersed polymer droplet by evaporation of dichloromethane formed an internal cavity in microsphere of polymer with drug. The micro balloons floated continuously over the surface of acidic dissolution media containing surfactant for more than 12 hours *in vitro*.

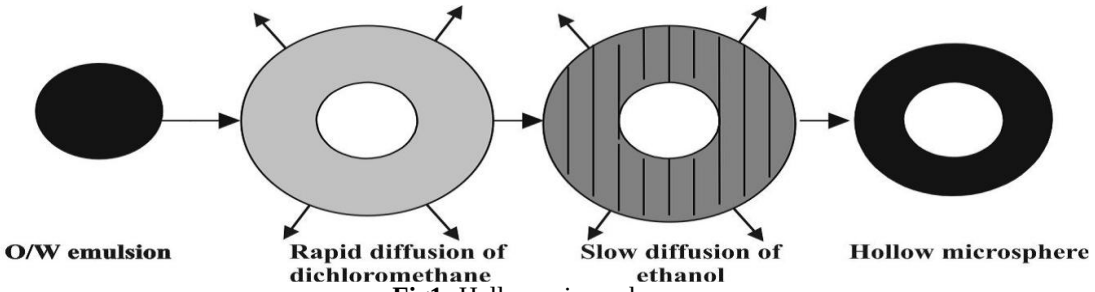

Fig1: Hallow microspheres

Advantages of FDDS:

- Improved drug absorption, because of increased GRT and more time spent by the dosage form at its absorption site.
- Controlled delivery of drugs.
  3. Minimizing the mucosal irritation due to drugs
- Treatment of gastrointestinal disorders such as gastro-esophageal reflux.

Disadvantages of FDDS:

- Gastric retention is influenced by many factors such as gastric motility, pH and presence of food. These factors are never constant and hence the buoyancy cannot be predicted.
- Drugs that cause irritation and lesion to gastric mucosa are not suitable to be formulated as floating drug delivery systems.

II. Materials and Methods

S.no	Materials
1.	Dipyridamole
2.	Guar Gum
3.	Xanthum Gum
4.	HPMC K15M
5.	Sodium bicarbonate
6.	Magnesium stearate
7.	Micro crystalline cellulose
8.	Talc

Analytical method development:

- **Determination of absorption maxima:**

A solution containing the concentration 10 µg/ ml drug was prepared in 0.1N HCl UV spectrum was taken using Double beam UV/VIS spectrophotometer. The solution was scanned in the range of 200 – 400.

2,1Drug – Excipient compatibility studies:

Formulation development of Tablets:

All the formulations were prepared by direct compression. The compression of different formulations is given in Table .The tablets were prepared as per the procedure given below and aim is to prolong the release of Dipyridamole. Total weight of the tablet was considered as 600mg.

Procedure:

- Dipyridamole and all other ingredients were individually passed through sieve no 60.
- All the ingredients were mixed thoroughly by triturating up to 15 min.
- The powder mixture was lubricated with talc.
- The tablets were prepared by using direct compression method.

Optimization of Sodium bicarbonate concentration:

Sodium bicarbonate was employed as effervescent gas generating agent. It helps the formulation to float. Various concentrations of sodium bicarbonate were employed; floating lag time and floating duration were observed. Based on the concentration of sodium bicarbonate was finalized and preceded for further formulations.

S.No	Excipient Name	EF1	EF2	EF3
1	Dipyridamole	300	300	300
2	HPMC K15 M	150	150	150
4	$NaHCO_3$	75	90	105
5	Mg.Stearate	6	6	6
5	Talc	6	6	6
7	MCC pH 102	Q.S	Q.S	Q.S
	Total weight	600	600	600

All the quantities were in mg.

Table1 : Optimization sodium bicarbonate concentration

Formulation No.	**Dipyrridamole**	**Xanthum gum**	**HPMC K15 M**	**Guar gum**	**$NaHCO_3$**	**Mag. Stearate**	**Talc**	**MCC pH 102**
F1	300	50			90	6	6	QS
F2	300	100			90	6	6	QS
F3	300	150			90	6	6	QS
F4	300	200			90	6	6	QS
F5	300		50		90	6	6	QS
F6	300		100		90	6	6	QS
F7	300		150		90	6	6	QS
F8	300		200		90	6	6	QS
F9	300			50	90	6	6	QS
F10	300			100	90	6	6	QS
F11	300			150	90	6	6	QS
F12	300			200	90	6	6	QS

All the quantities were in mg, Total weight is 600 mg.

Table 2 : Formulation composition for floating tablets

2.2 Evaluation of post compression parameters for prepared Tablets

The designed compression tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content. The optimised tablets were subjected to In vitro buoyancy studies, In vitro drug release studies and application of release rate kinetics to dissolution data (Zero order, First order, Higuchi release model, Korsmeyer and Peppas release model, and Hixson-Crowell release model)

III. Results and Discussions

The present study was aimed to developing gastro retentive floating tablets of Dipyridamole using various natural polymers. All the formulations were evaluated for physicochemical properties and invitro drug release studies.

3.1. Analytical Method

Graph of Dipyridamole was taken in Simulated Gastric fluid (pH 1.2) at 288 nm.

Conc [µg/l]	**Abs**
2	0.131
4	0.252
6	0.367
8	0.479
10	0.619

Table 3: Observations for graph of Dipyridamolein 0.1N HCl (288 nm)

Figure 2: Standard graph of Dipyrridamole in 0.1N HCl

3.2. Drug – Excipient compatability studies

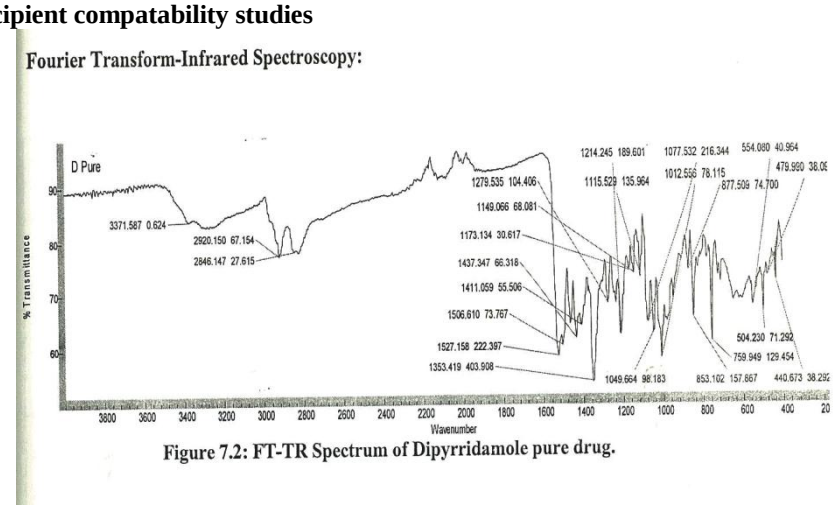

Figure 7.2: FT-TR Spectrum of Dipyrridamole pure drug.

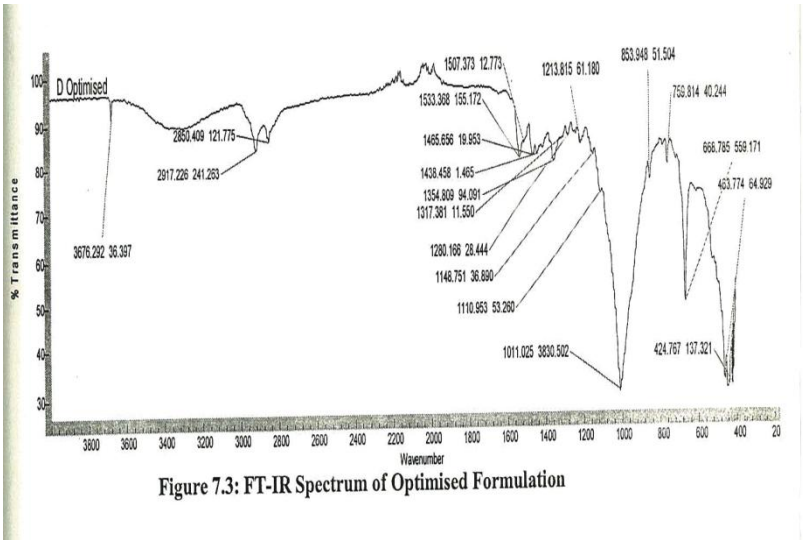

Figure 7.3: FT-IR Spectrum of Optimised Formulation

3.4. Preformulation parameters of powder blend

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
F1	26.01	0.45	0.54	16.6	1.2
F2	24.8	0.50	0.61	18.03	1.22
F3	22.74	0.47	0.58	18.96	1.23
F4	25.33	0.48	0.59	18.64	1.22
F5	26.24	0.51	0.62	17.74	1.21
F6	26.12	0.50	0.61	18.03	1.22
F7	27.08	0.49	0.60	18.33	1.22
F8	25.12	0.48	0.58	17.24	1.20
F9	25.45	0.46	0.57	19.28	1.23
F10	27.51	0.45	0.54	16.66	1.2
F11	25.83	0.50	0.61	18.03	1.22
F12	26.93	0.51	0.60	15	1.17

Table 4: Pre-formulation parameters of blend

Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.45 to 0.51(gm/cm3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.54 to 0.62 showing the powder has good flow properties. The compressibility index of all the formulations was found to be ranging from 15 to 18 which show that the powder has good flow properties. All the formulations has shown the hausner ratio ranging less than 1.25 indicating the powder has good flow properties.

3.5. Optimization of sodium bicarbonate concentration:

Three formulations were prepared with varying concentrations of sodium bicarbonate. The formulation containing sodium bicarbonate in 90mg concentration showed less floating lag time of 4 min and the tablet was in floating condition for more than 12 hours.

3.6. Quality Control Parameters For tablets:

Tablet quality control tests such as weight variation, hardness, and friability, thickness, and drug release studies in different media were performed on the tablets.

Formulation code	Weight variation(mg)	Hardness (kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)	Flaoting lag time (min)
F1	612.5	4.5	0.52	4.8	99.76	4.0
F2	605.4	4.2	0.54	4.9	99.45	4.2
F3	598.6	4.4	0.51	4.9	98.34	4.5
F4	610.6	4.5	0.55	4.9	99.87	4.1
F5	609.4	4.4	0.56	4.7	99.14	4.0
F6	610.7	4.2	0.45	4.5	98.56	4.4
F7	602.3	4.1	0.51	4.4	98.42	4.5
F8	601.2	4.3	0.49	4.7	99.65	4.6
F9	598.3	4.5	0.55	4.6	99.12	4.7
F10	600.5	4.5	0.56	4.6	98.56	4.5
F11	602.5	4.5	0.58	4.8	99.45	4.3
F12	600.6	4.5	0.63	4.7	98.54	4.4

Table 5. Invitro quality control parameters for tablets

All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits.

***3.7. In-Vitro* Drug Release Studies**

TIME (hr)	CUMULATIVE PERCENT DRUG DISSOLVED			
	F1	F2	F3	F34
0.5	21.73	18.52	15.43	12.53
1	59.23	37.47	28.31	25.97
2	84.9	59.93	40.36	34.89
3	99.873	65.85	58.48	45.76
4		77.54	70.21	56.38
5		99.55	82.54	64.2
6			96.64	69.06
7				77.52
8				87.88
9				98.45

Table 6: Dissolution Data of Dipyrridamole Tablets Prepared With Xanthum gum In Different Concentrations

Fig 3: Dissolution profile of Dipyrridamole floating tablets (F1, F2, F3,F4 formulations).

TIME (hr)	CUMULATIVE PERCENT DRUG DISSOLVED			
	F5	F6	F7	F8
0.5	23.45	20.42	17.48	14.62
1	36.26	29.73	25.37	19.86
2	52.16	35.63	32.28	26.35
3	70.01	40.04	38.21	31.45
4	87.26	49.25	44.38	39.80
5	96.10	56.33	50.83	44.25
6		62.41	58.32	52.24
7		70.84	64.39	58.73
8		88.80	71.71	64.34
9		97.58	79.46	72.52
10			85.39	80.17
11			97.38	89.75
12				97.33

Table 7: Dissolution Data of Dipyrridamole Tablets Prepared With HPMC K15M In Different Concentrations

Fig4: Dissolution profile of Dipyrridamole floating tablets (F5, F6, F7,F8 formulations).

TIME (hr)	CUMULATIVE PERCENT DRUG DISSOLVED			
	F9	F10	F11	F12
0.5	17.81	14.89	12.74	10.21
1	26.02	20.04	18.27	14.87
2	32.70	26.43	25.48	22.19
3	40.32	35.65	30.28	28.66
4	48.25	44.18	38.47	33.32
5	56.28	51.81	44.37	40.06
6	64.92	53.89	49.29	47.13
7	75.08	60.53	55.38	53.63
8	80.44	79.43	61.25	58.71
9	97.22	76.83	68.47	63.34
10		86.98	74.21	69.27
11		96.54	80.43	72.86
12			89.34	80.97

Table 8: Dissolution Data of Dipyrridamole Tablets Prepared With Guar Gum In Different Concentrations

Fig 5: Dissolution profile of Dipyrridamole floating tablets (F9, F10, F11,F12 formulations)

From the dissolution data it was evident that the formulations prepared with Xanthum gum as polymer were unable to retard the drug release up to desired time period i.e., 12 hours. Whereas the formulations prepared with HPMC K15M retarded the drug release in the concentration of 200 mg showed required release pattern i.e., retarded the drug release up to 12 hours and showed maximum of 97.33 % in 12 hours (Formulation F6) with good floating lag time and floating buoyancy time. The formulations prepared with Guar gum showed more retardation even after 12 hours they were not shown total drug release. Hence they were not considered.

Application of Release Rate Kinetics to Dissolution Data:

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi and Korsmeyer-Peppas release model.

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM% RELEASE	PEPPAS log Q/100
0	0	0			2.000			
14.62	0.5	0.707	1.165	-0.301	1.931	29.240	0.0684	-0.835
19.86	1	1.000	1.298	0.000	1.904	19.860	0.0504	-0.702
26.35	2	1.414	1.421	0.301	1.867	13.175	0.0380	-0.579
31.45	3	1.732	1.498	0.477	1.836	10.483	0.0318	-0.502
39.8	4	2.000	1.600	0.602	1.780	9.950	0.0251	-0.400
44.25	5	2.236	1.646	0.699	1.746	8.850	0.0226	-0.354
52.24	6	2.449	1.718	0.778	1.679	8.707	0.0191	-0.282
58.73	7	2.646	1.769	0.845	1.616	8.390	0.0170	-0.231
64.34	8	2.828	1.808	0.903	1.552	8.043	0.0155	-0.192
72.52	9	3.000	1.860	0.954	1.439	8.058	0.0138	-0.140
80.17	10	3.162	1.904	1.000	1.297	8.017	0.0125	-0.096
89.75	11	3.317	1.953	1.041	1.011	8.159	0.0111	-0.047
97.33	12	3.464	1.988	1.079	0.427	8.111	0.0103	-0.012

Table 9: Release kinetics data for optimised formulation (F6)

Fig 6 : Zero order release kinetics graph
Fig 7 : Higuchi release kinetics graph
Fig 8: Kars mayer peppas graph
Fig 9: First order release kinetics graph

From the above graphs it was evident that the formulation 86 was followed Zero order release mechanism.

IV. Conclusion

In the present research work the gastro retentive floating matrix formulation of Dipyrridamole by using various hydrophilic polymers. Initially analytical method development was done for the drug molecule. Absorption maxima was determined based on that calibration curve was developed by using different concentrations. Gas generating agent sodium bicarbonate concentration was optimized. Then the formulation was developed by using different concentrations of polymers of various natural polymers. The formulation blend was subjected to various preformualation studies, flow properties and all the formulations were found to be good

indicating that the powder blend has good flow properties. Among all the formulations the formulations prepared by using Xanthum gum were unable to produce desired drug release; they were unable to retard drug release up to 12 hours. The formulations prepared with HPMC K15 M retarded the drug release up to 12 hours in the concentration of 200 mg (F8).The formulations prepared with Guar gum were also retarded the drug release for more than 12 hours. Hence they were not considered. The optimized formulation dissolution data was subjected to release kinetics, from the release kinetics data it was evident that the formulation followed Zero order mechanism of drug release.

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