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Formulation optimization and *in vitro* evaluation for the gastro retentive tablets of Labetolol

Sravanthi Todasam and Nagarajan Srinivasan

Srisarada college of pharmacy. (Jntuh)Anantharam, Bhongir, Nalgonda, Telangana, India.

***Corresponding author: Sravanthi Todasam**

ABSTRACT

The controlled gastric retention of solid dosage forms may be achieved by the mechanisms of mucoadhesion, flotation, sedimentation, expansion, modified shape systems, or by the simultaneous administration of pharmacological agent that delay gastric emptying. Based on these approaches, classification of floating drug delivery systems (FDDS) has been described in detail. Floating granules were prepared by using Direct Compression technique. The oral bioavailabilty of Labetolol has been reported to be about 25%. Gastric floating drug delivery is one approach where the gastro intestinal residence time is prolonged because of the floating behavior. In the present study the formulations were prepared by using different proportions of polymer. The prepared formulations were evaluated for different physicochemical characteristics such as thickness and diameter, drug content, weight variation, hardness, friability. The release characteristics of the formulation were studied in *in-vitro* conditions. The IR spectrum of pure drug and drug-polymer mixture revealed that there was no interaction between polymer and drug. The prepared floating tablet is industrially feasible method. Bulk density and tapped density shown good packability and Carr's index results shown excellent compressibility. Formulation F16 containing combination of Metalose SR and Manucol was found to release a maximum of 97.2431% at the 12th hour.

Keywords: Floating Tablets, Gastroretentive Systems, Labetolol

INTRODUCTION

Oral delivery of drugs is by far the most preferable route of drug delivery due to the ease of administration, patient compliance and flexibility in formulation, etc.[1] It is evident from the recent scientific and patent literature that an increased interest in novel dosage forms that are retained in the stomach for a prolonged and predictable period of time exists today in academic and industrial research groups.[2] One of the most feasible approaches for achieving a prolonged and

predictable drug delivery profile in the GI tract is to control the gastric residence time (GRT). Dosage forms with a prolonged GRT, i.e. gastro retentive dosage forms (GRDFs), will provide us with new and important therapeutic options. GRDFs extend significantly the period of time over which the drug may be released.[3] Thus, they not only prolong dosing intervals, but also increase patient compliance beyond the level of existing controlled release dosage forms.[4] This application is especially effective in delivery of sparingly soluble and insoluble drugs.[5] It is known that, as the solubility of a drug decreases, the time available for drug dissolution becomes less adequate and thus the transit time becomes significant factor affecting drug absorption.[6] To address this, oral administration of sparingly soluble drugs are carried out frequently, often several times per day.[7]

Gastro retentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines.[8] Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients. The controlled gastric retention of solid dosage forms may be achieved by the mechanisms of mucoadhesion, flotation, sedimentation, expansion, modified shape systems, or by the simultaneous administration of pharmacological agent that delay gastric emptying. Based on these approaches, classification of floating drug delivery systems (FDDS) has been described in detail. In vivo/in vitro evaluation of FDDS has been discussed by scientists to assess the efficiency and application of such systems.[9] Several recent examples have been reported showing the efficiency of such systems for drugs with bioavailability problems.[10]

MATERIALS AND METHODS

Labetolol (Spectrum Pharma, Hyderabad), Celkol, Manucol (Ontop pharmaceuticals, Bangalore), Metalose SR (S.D fine chemicals, Boisar), Sodium bicarbonate (S.D fine chemicals, Boisar), Citric acid (S.D fine chemicals, Boisar), Lactose (S.D fine chemicals, Boisar), Magnesium stearate (S.D fine chemicals, Boisar), Hydrochloric acid (S.D fine chemicals, Boisar), Alcohol IP (S.D fine chemicals, Boisar), Distilled water.

FORMULATION OF FLOATING TABLETS

Direct Compression Technique

Floating granules were prepared by using Direct Compression technique. The polymers, MCC, Ammonium bicarbonate, citric acid and the active ingredient were weighed and mixed thoroughly. All the ingredients were mixed according to weights. The granules were dried in a conventional hot air oven. The dried granules were sieved through 40/60 meshes. Magnesium stearate & Talc were added as a lubricant and the granules were compressed into tablets using 16 station rotary punch tablet compression machine.

Table No. 1 FORMULA OF FABRICATED FLOATING TABLETS

	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16	F17	F18
LABETOLOL	150	150	150	150	150	150	150	150	150	150	150	150	150	150	150	150	150	150
AM. BICARBONATE	20	20	20	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40
C. ACID	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20
METALOSE SR	40	****	****	40	****	****	80	****	****	120	****	****	160	****	****	80	80	****
MANNUCOL	****	40	****	****	40	****	****	80	****	****	120	****	****	160	****	80	****	80
CELKOL	****	****	40	****	****	40	****	****	80	****	****	120	****	****	160	****	80	80
AEROSIL	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
MCC	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
MG STEARATE	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
TALC	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
WT	400	400	400	400	400	400	400	400	400	400	400	400	400	400	400	400	400	400

RESULTS AND DISCUSSION

The oral bioavailabilty of Labetolol has been reported to be about 25%. Gastric floating drug delivery is one approach where the gastro intestinal residence time is prolonged because of the floating behavior. Metalose SR, Celkol and Manucol were used as swellable polymers and chosen because it is widely used as a low-density hydrocolloid system upon contact with water a hydrogel layer would be formed to act as a gel boundary for the delivery system, but it would fail to retard the release of drug through the matrix because of its solubility in stomach pH. Citric acid has stabilizing effect and ammonium bicarbonate is used as buoyancy-imparting agent.

In the present study the formulations were prepared by using different proportions of polymer. The prepared formulations were evaluated for different physicochemical characteristics such as thickness and diameter, drug content, weight variation, hardness, friability. The release characteristics of the formulation were studied in *in-vitro* conditions.

Compatibility study of Labetolol by FTIR

FTIR spectras of pure Labetolol, blend of polymer with drug were determined (figure 13). Labetolol showed that the principle IR peaks 3377.39, 3090.28, 2923.76, 2620.71, 1701.51, 1623.93, 1312.68, 1187.2. Labetolol with excipients had shown 3093.83, 2933.00, 2620.47, 1708.66, 1625.66, 1386.80, 1310.90, and 944.54. The IR spectra of all the tested samples showed the prominent characterizing peaks of pure Labetolol which confirm that interactions between drug, polymers were unlikely to occur. (Table. 1).

Evaluation of precompression parameters of formulated granules

Formulation of proper granule blend is the key factor in the production of tablet dosage form involving floating extended release of drug from matrix type particle. Physical parameters such as specific surface area, shape, hardness, surface characteristics and size can be significantly affect the rate of dissolution of drugs. The formulated blends of different formulations F1 to F18 were evaluated for angle of repose, tapped density, bulk density, Carr's index and Hausner ratio. The results of angle of repose (<30) indicates good flow properties of entire formulated granule blend. The compressibility index value were recorded and were resulted in good to excellent flow properties. (Table.1).

Hardness

The prepared tablets in all the formulations possessed good mechanical strength sufficient hardness. The hardness of the tablets ranges from 3.99 to 4.86. (Table.1).

Thickness & Diameter

The thickness and diameter of the tablets were found to be in the range of 7.01mm to 7.11mm and 9.42 to 9.44mm respectively. (Table.1).

Friability

The friability loss of the tablet was found to be 0.26 to 0.88% determined by using Roche Friabilator. All batches of tablets passed the test and are within the limits. It indicated that the tablets were mechanically stable. (Table. 1).

Weight variation test

All the batches of tablets were found to pass the weight variation test. The percentage deviation of the individual tablet weight from the average tablet weight was found to be within the I.P limits ± 7.5%. (Table. 1).

Drug content uniformity

The drug content uniformity was examined as per I.P specification. All the batches of tablets were found to comply with uniformity of content test. None of the individual drug content values were out side the average content values. (Table. 1).

Swelling index

In formulations containing Metalose SR the swelling index ranges from 2.0 to 2.2, the formulations containing Celkol the swelling index ranges from 1.3 to 1.9 and the formulations containing Manucol ranges from 2.0 to 2.3. (Table 1).

IN VITRO BUOYANCY STUDIES

The *in vitro* buoyancy studies were determined by the floating lag time. The tablets

were placed in a 100 ml beaker containing 0.1N HCL. The time required for the tablet to rise to the surface for floating was determined as the floating lag time and further floating duration of all tablets was determined by visual observation. The results for floating lag time are presented in Table No. From the study of floating properties, it was observed that floating lag time ranges from 59 to 110 sec and tablets of batches ranging from F1 to F8 & F13 to F18 remain buoyant up to 12 hours and the tablets of batches ranging from F9 to F12 remain buoyant up to 8 hours, during which the tablets lost their integrity and the size of the swollen matrix gel drastically reduced. Floating lag time was observed that the range of 59 to 110 seconds for all the formulations. Duration of floating for prepared tablets of each batch remained buoyant up to 12 hours, during which the tablets lost their integrity and the size of the swollen matrix gel drastically reduced. (Table. 1)

Table No. 2 FLOATING PROPERTIES OF TABLETS

Formulation Code	Buoyancy lag time	Duration of buoyancy
F1	92	> 12
F2	87	> 12
F3	98	> 12
F4	105	> 12
F5	59	> 12
F6	88	> 12
F7	109	> 12
F8	98	> 12
F9	110	8
F10	97	8
F11	105	8
F12	98	8
F13	99	> 12
F14	104	> 12
F15	65	> 12
F16	79	> 12
F17	97	> 12
F18	99	> 12

Table No. 3 Evaluation Data of Preformulation Studies-1

Formulation Code	DERIVED PROPERTIES	
	Bulk density (g/ml) ± S.D	Tapped density(g/ml) ± S.D
F1	0.4327 ± 0.00358	0.5263 ± 0.0052
F2	0.4414 ± 0.01137	0.5068 ± 0.0117
F3	0.4414 ± 0.01137	0.5175 ± 0.0151
F4	0.4479 ± 0.01137	0.5090 ± 0.0289
F5	0.4617 ± 0.01252	0.5556 ± 0.0117
F6	0.4404 ±0.0113	0.5263 ± 0.0052
F7	0.4414 ± 0.01137	0.5175 ± 0.01518
F8	04414 ± 0.01137	0.4921 ± 0.01374
F9	0.4167 ± 0.01137	0.4762 ± 0.0289
F10	0.41670 ± 0.01252	0.4901 ± 0.0172
F11	0.4167 ± 0.00358	0.4801 ± 0.0172
F12	0.400 ± 0.01178	0.4696 ± 0.0125
F13	0.441 ± 0.01124	0.5068 ± 0.0117
F14	0.4514 ± 0.01137	0.5175 ± 0.0151
F15	0.4679 ± 0.01137	0.5090 ± 0.0289
F16	0.4517 ± 0.01252	0.5556 ± 0.0117
F17	0.4304 ±0.0113	0.5263 ± 0.0052
F18	0.4454 ± 0.01137	0.5175 ± 0.01518

Table No. 4 Evaluation Data of Preformulation Studies-2

	FLOW PROPERTIES		
Formulation	Carr's index	Hausner's ratio	Angle of repose
F1	17.3167 ± 1.270	1.2092 ± 0.0021	27.4056 ± 0.5775
F2	13.2400 ± 0.3469	1.1483 ± 0.0030	27.5533 ± 3.0457
F3	15.9400 ± 1.5114	1.1903 ± 0.0348	28.0715 ± 0.8658
F4	11.990 ± 1.8578	1.1371 ± 0.0362	27.0092 ± 0.7691
F5	16.8967 ± 1.2574	1.2038 ± 0.0321	28.3280 ± 0.7465
F6	16.1400 ± 1.1650	1.1929 ± 0.0302	28.1322 ± 0.4142
F7	14.6900 ± 2.5114	1.1728 ± 0.0328	27.897 ± 04333
F8	9.8896 ± 1.8392	1.1105 ± 0.0354	28.7632 ± 0.7504
F9	12.49 ± 0.9878	1.1455 ± 0.0435	28.1353 ± 0.4191
F10	14.900 ± 1.0484	1.1761 ± 0.0412	29.8967 ± 0.7654
F11	13.14 ± 1.0484	1.1522 ± 0.0412	28.1353 ± 0.4132
F12	14.6633 ± 1.3151	1.1724 ± 0.0312	27.4422 ± 1.5192
F13	14.5400 ± 1.5114	1.1803 ± 0.0348	26.0715 ± 0.8658
F14	10.790 ± 1.8578	1.1471 ± 0.0362	25.0092 ± 0.7691
F15	15.7967 ± 1.2574	1.1738 ± 0.0321	29.3280 ± 0.7465
F16	15.2100 ± 1.1650	1.1829 ± 0.0302	26.1322 ± 0.4142
F17	13.6500 ± 2.5114	1.1628 ± 0.0328	28.897 ± 04333
F18	11.8896 ± 1.8392	1.1305 ± 0.0354	29.7632 ± 0.7504

In vitro dissolution study

Dissolution apparatus USP type II paddle method was used to carry out *in-vitro* drug release studies on the prepared batches of floating tablets with a stirring speed of 50 rpm at $37^{O}C \pm 0.5$ in 900 ml of (pH 1.2) simulated gastric fluid for 12 hours.

Here in *in vitro* Dissolution Studies we selected first 3 formulations with 20 mg of Ammonium bicarbonate and 20 mg of Citric acid but these formulations were not float so we changed 20 mg of Ammonium bicarbonate to 40 mg with the 10 % Polymer.

Formulations F4, F5 & F6 which are prepared with 10% of polymers like Metalose SR, Mannucol

and Celkol respectively shows 100% drug release up to 4 hrs, in formulations F7, F8 & F9 were prepared with 20% of Polymer concentration for these formulations 100% drug release shows in 6 hrs. Next formulations F10, F11 & F12 were prepared with 30 % of polymer these formulations releases 100% drug in 10hrs for F10 & F11 and F12 releases in 9hrs itself. Again increased polymer concentration to 40% for formulations F13, F14& F15 these formulations showed satisfactory drug release for 12hrs.

So, all the above formulations F4 to F15 were prepared with single concentration of polymer and in next formulations we combine the polymers with the combined concentration of 20%+20% for F16, F17& F18, these formulations which are formulated with the combination of polymers shows better results than the formulations which are prepared individually, in all the formulations F16 formulation prepared with the combination of Metalose SR & Mannucol showed satisfactory results.

COMPARISON GRAPH FOR FORMULATIONS FROM F4 to F18

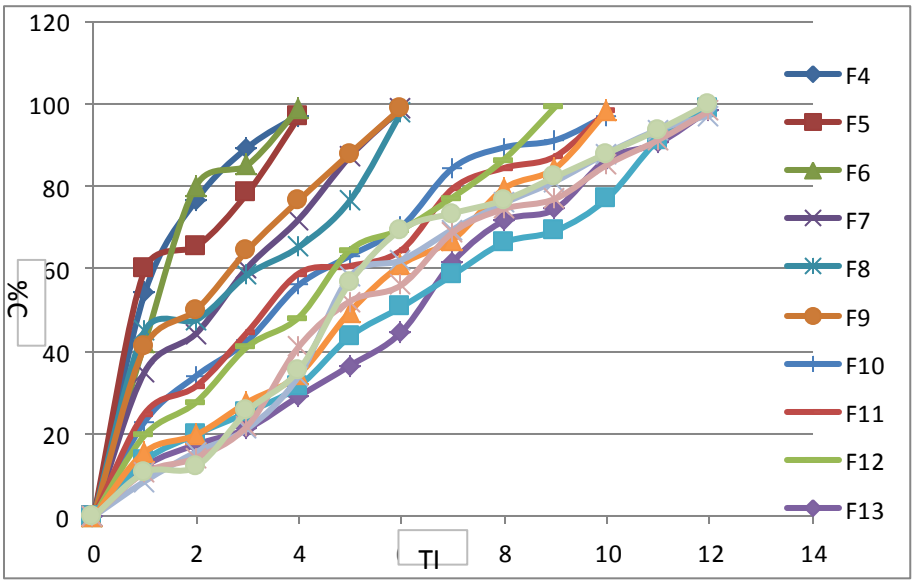

Figure: 1

Analysis of samples

5ml of aliquots were withdrawn at time intervals of 1h for 12h. The samples were replaced by equivalent volume of dissolution medium. The samples were analysed spectrophotometrically at 289 nm for the drug content against blank. The mean percentage of Labetolol released at various time intervals was calculated and plotted against time.

Stability study

The stability study was carried out using the best batch. After an interval of 90 days, samples were withdrawn and retested for drug content, buoyancy lag-time, buoyancy time. The results of these formulations remained stable for three months. (Table. 4).

CONCLUSION

Over the years, various attempts has been made to control the time course of drug in the body through variety of drug modifications and dosage forms. One of the most feasible approaches for achieving a prolonged and predictable drug delivery profile in the GI tract is to control the gastric residence time (GRT). The approach of the present study was to formulate floating tablets of Labetolol and hence forth evaluate the release profiles of these formulations. The IR spectrum of pure drug and drug-polymer mixture revealed that there was no interaction between polymer and drug. The prepared floating tablet is industrially feasible method. Bulk density and tapped density shown good packability and Carr's index results shown excellent

compressibility. Formulation F16 containing combination of Metalose SR and Manucol was found to release a maximum of 97.2431% at the 12^{th} hour.

Comparison of all formulation of Labetolol revealed the fact that developed formulation F16 showed comparable release characteristics, thus it may have fair clinical efficacy. Hence, the formulation F16 has met the objectives of the present study. The result of stability studies indicates that these formulations remained stable for three months. Formulation F16 holds promise for further *in vivo* studies, which can be extrapolated for the development of floating drug delivery system.

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