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Research Article

PREPARATION AND EVALUATION OF PULSATILE DRUG DELIVERY SYSTEM CONTAINING TERBUTALINE SULPHATE

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ABSTRACT
In this study, investigation of an oral colon specific, pulsatile device to achieve time and/or site specific release of terbutaline sulphate, based on chronopharmaceutical consideration. The basic design consists of an insoluble hard gelatin capsule body, filled with ethyl cellulose microcapsules of terbutaline sulphate and sealed with a hydro gel plug. The entire device was enteric coated, so that the variability in gastric emptying time can be overcome and a colon-specific release can be achieved. The terbutaline sulphate microcapsules were prepared in three batches, with Ethyl cellulose and dichloromethane (1:2) by varying drug to polymer ratio and evaluated for drug content and in vitro release profile and from the obtained results; one better formulation was selected for further fabrication of pulsatile capsule. Different hydrogel polymers were used as plugs, to maintain a suitable lag period and it was found that the drug release was controlled by the proportion of polymers used. Programmable pulsatile, colon-specific release has been achieved from a capsule device over a 2–24 h period, consistent with the demands of chronotherapeutic drug delivery.

KEYWORDS: Pulsatile system, Ethyl Cellulose.

INTRODUCTION
Research on site-specific and temporal control of drug delivery systems is receiving a major impetus towards the development of new and/or improved drug therapies. Among modified-release oral dosage forms, increasing interest has currently turned to systems designed to achieve time specific (delayed, pulsatile) and site-specific delivery of drugs. These systems constitute a relatively new class of devices the importance of which is especially connected with the recent advances in chronopharmacology. In the last decade numerous studies in animals as well as clinical studies have provided convincing evidence, that the pharmacokinetics and/or the drug's effects-side effects can be modified by the circadian time and/or the timing of drug application within 24 h of a day. On the other hand, colon-specific drug delivery systems (CDDS) have been developing as one of the site-specific drug delivery systems. Along with many applications in local and systemic delivery of drugs the CDDS would also be advantageous when a delay in absorption is desirable from a therapeutic point of view as for the treatment of diseases that have peak symptoms in the early morning and that exhibit circadian rhythm, such as nocturnal asthma, angina and rheumatoid arthritis. So by developing the pulsatile device for specific colonic delivery, plasma peak is obtained at an optimal time, number of doses per day can be reduced; saturable first pass metabolism and tolerance development can also be avoided.

MATERIAL AND METHOD
Terbutaline sulphate was obtained as gift sample from Concept pharma Aurangabad. Ethyl Cellulose and dichloromethane were purchased commercially, whereas HPMC, Gaur gum and HPC were obtain as gift sample from Shreya Pharmaceutical Aurangabad.

Method of preparation (Microcapsule)

Three various formulation parameter were adopted for the preparation of microcapsule, which is mention in the below table (after the references).

All the three formulation were designed to improve the percentage yield of the formed microcapsule. The dispersion which was prepared in all the three mention formulation were kept under stirring at 500 rpm for 8 hrs and after the stirring was completed the formed microcapsule were filtered and were dried under the sunlight. The prepared microcapsules were evaluated for further studies.

Formulation of pulsatile drug delivery system

The bodies and caps hard gelatin capsules of were separated manually. Microcapsules equivalent to 200 mg for formulation 1, 320 mg for formulation 2 and 400 mg for formulation 3 of terbutaline sulphate were accurately weighed and filled into the treated bodies by hand filling. The capsules containing the microcapsules were then plugged with different amounts (40, 50 and 70 mg) of various polymers, i.e., HPMC, gaur gum and HPC.The joint of the capsule body and cap was sealed with a small amount of the 5% ethyl cellulose ethanolic solution. The sealed capsules were completely coated by dip coating method 10% HPMC solution plasticized with dibutylphthalate (0.75%), to prevent variablegastric emptying. Coating was repeated until 10% increase in weight is obtained. % weight gain of the capsules before and after coating was determined.

Dissolution Studies

Dissolution studies were carried out by using USP paddle dissolution test apparatus. Capsules were tied to paddle with a cotton thread so that the capsule should be immersed completely in dissolution media but not float. In order to simulate the pH changes along the GI tract, three dissolution media with pH 1.2, 7.4 and 6.8 were sequentially used, referred to as sequential pH change method When performing experiments, the pH 1.2 medium was first used for 2 h (since the average gastric emptying time is 2 h), then removed and the fresh pH 7.4 phosphate buffer saline (PBS) was added. After 3 h (average small intestinal transit time is 3 h), the medium was removed and fresh pH 6.8 dissolution medium was added for subsequent hours. Nine hundred milliliters of the dissolution medium was used at each time. Rotation speed was 100 rpm and temperature was maintained at 37±0.5 ◦C. Capsules were tied to paddle with a cotton thread in each dissolution vessel to prevent floating. Five milliliters of dissolution media was withdrawn at predetermined time intervals and fresh dissolution media was replaced. The withdrawn samples were analyzed at 296 nm, by UV absorption spectroscopy and the cumulative percentage release was calculated over the sampling times.

RESULT AND DISCUSSION

During the formulation of the microcapsule it was observed that as concentration of the ethyl cellulose was increased the % yield of the microcapsule was increased. The reason must be the simple as the amount of the dissolved solid was increased the % yield was increased. In the pulsatile formulation all the three polymer which were used as the plugging agent to get the control release out of that the capsule which was plugged with HPC gave the highest drug release than the gaur gum and the HPMC. The simple reason behind this must be that the viscosity of the HPMC was the most due to which there must be the slow release of the drug compare to two others.

CONCLUSION

The pulsatile dosage form was successfully formulated. In all the three formulation it was observed that drug release was good but it was highest in the HPC plugged capsule.

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Table 1 (Formulation 1)

Sr. No.	Ingredient	Quantity
1.	Ethyl cellulose	10 gm
2.	Terbutaline Sulphate	5 gm
3.	Dichloromethane	50 ml

Table 2 (Formulation 2)

Sr. No.	Ingredient	Quantity
1.	Ethyl cellulose	15 gm
2.	Terbutaline Sulphate	5 gm
3.	Dichloromethane	100 ml

Table 3 (Formulation 3)

Sr. No.	Ingredient	Quantity
1.	Ethyl cellulose	20 gm
2.	Terbutaline Sulphate	5 gm
3.	Dichloromethane	150 ml

Table 4 (Formulation 4)

Sr. No.	Ingredient	Quantity (mg)
1.	Empty gelatin capsule	60
2.	Microcapsule	320
3.	Plugged Gaur gum	50

Table 5 (Formulation 5)

Sr. No.	Ingredient	Quantity (mg)
1.	Empty gelatin capsule	60
2.	Microcapsule	200
3.	Plugged HPMC	40

Table 6 (Formulation 6)

Sr. No.	Ingredient	Quantity (mg)
1.	Empty gelatin capsule	60
2.	Microcapsule	320
3.	Plugged HPC	70

Table 7 Evaluation of microcapsule for (formulation 1)

Sr. no	**Parameters**	**Result**
1	Weight of microcapsules	1.2 gm
2	% Yield	24 %
3	Shape	Spherical
4	Hausner's ratio	1.0335
5	Carr's index	3.24
6	Angle of repose of microcapsule	31^0

Table 8 Evaluation of microcapsule for (formulation 2)

Sr. no	Parameters	Result
1	Weight of microcapsules	3.6 gm
2	% Yield	72 %
3	Shape	Spherical
4	Hausner's ratio	1.0335
5	Carr's index	3.08
6	Angle of repose of microcapsule	24.39^0

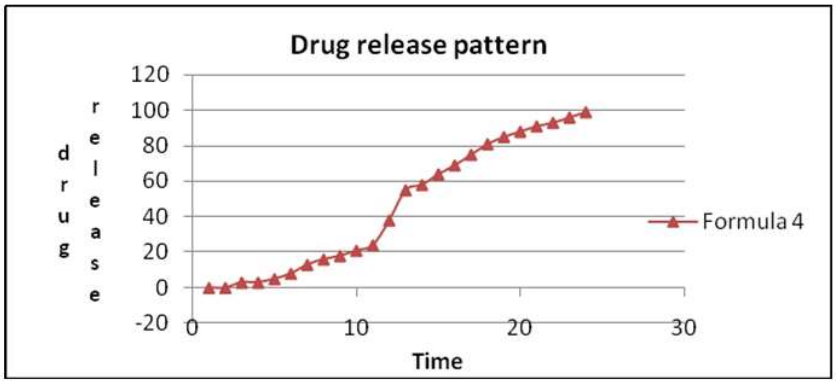
Table 9 Evaluation of microcapsule for (formulation 3):

Sr. no	Parameters	Result
1	Weight of microcapsules	4.5 gm
2	% Yield	90 %
3	Shape	Spherical
4	Hausner's ratio	1.0335
5	Carr's index	3.24
6	Angle of repose of microcapsule	22^0

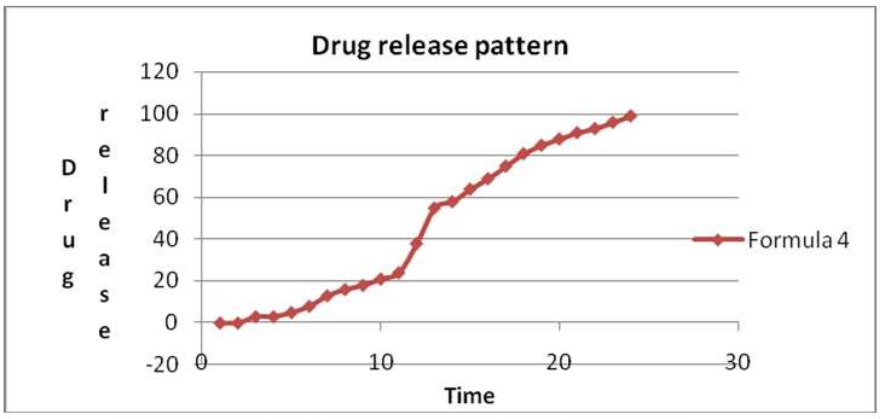
Table 9: Cumulative % drug release Dissolution Profile

Time (hr)	Formula 4	Formula 5	Formula 6
1	0	0	0
2	0	0	0
3	3	2	3
4	3	2	3
5	5	5	5
6	9	10	8
7	11	11	13
8	13	13	16
9	21	23	18
10	28	30	21
11	34	36	24
12	36	42	38
13	45	48	55
14	51	55	58
15	56	61	64
16	64	67	69
17	67	72	75
18	73	77	81
19	77	81	85
20	78	84	88
21	81	85	91
22	83	88	93

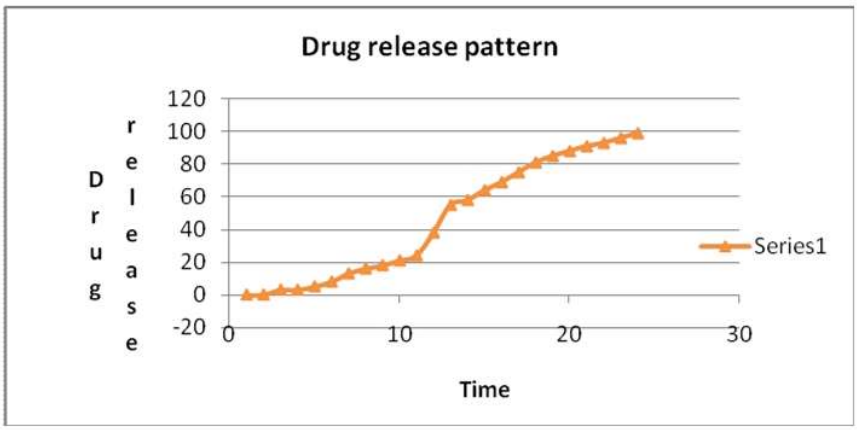
23	84	89	96
24	84	93	99

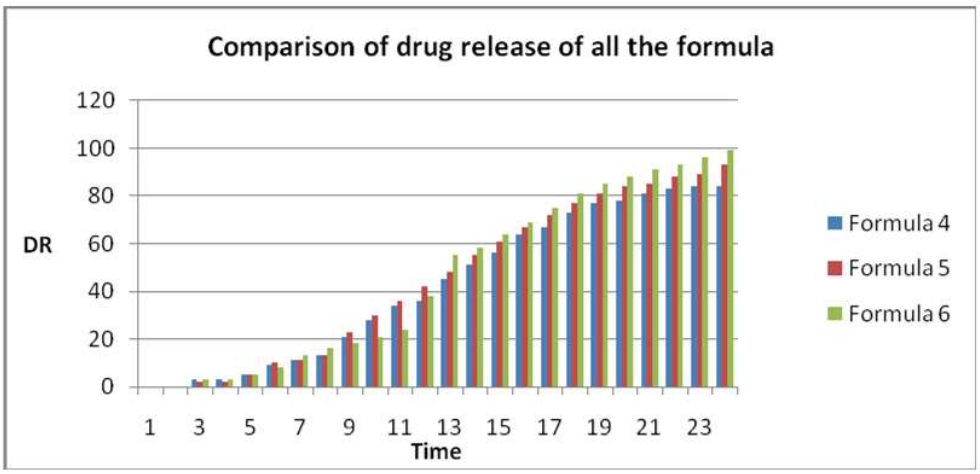


Dissolution Pattern for Formulation 4(fig 1)



Dissolution Pattern for Formulation 4(fig 1)





Drug Release Comparison of all the Formula

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