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RESEARCH ARTICLE

FORMULATION AND EVALUATION OF SODIUM ALGINATE AND HPMC MICROBEADS AS A CARRIER FOR THE CONTROLLED RELEASE OF CLONIDINE

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Abstract:

Clonidine Hydrochloride a centrally acting sympatholytic and Imidazoline-derivative hypotensive agent; selective α2-adrenergic agonist. It stimulates alpha2-adrenergic receptors in the brainstem to decrease sympathetic nervous system outflow. It is also administered epidurally to treat pain. The objective of the work was to design multiple unit dosage form as microbeads of a drug meant for management of anxiety and hypertensive disorder. Microbeads offers numerous advantages for releasing one of the drugs or part of the same drug immediately while remaining drug or parts of the same can be sustained release. Microbeads of Clonidine Hydrochloride obtained utilizing orifice ionic gelation technique using HPMC and sodium aliginate as a polymer with various ratios. Prepared beads were evaluated for drug entrapment, drug content, *in-vitro* release, release kinetic and stability study. particle size of optimized beads was determined by SEM.

Key Clonidine, microbeads, HPMC, sodium alginate, ionic gelation technique.

INTRODUCTION:

Oral drug delivery is the most desirable and preferred method of administering therapeutic agents for their systemic effects. In addition, the oral medication is generally considered as the first avenue investigated in the discovery and development of new drug entities and pharmaceutical formulations, mainly because of patient acceptance, convenience, and cost effective manufacturing process. For many drug substances conventional immediate release formulations provide clinically effective therapy while maintaining the required balance of pharmacokinetic and pharmacodynamic profiles with acceptable level of safety to the patient1.Multiple unit dosage forms such as microspheres or micro beads have gained in popularity as oral drug delivery systems because of more uniform distribution of the drug in the gastrointestinal tract, more uniform drug absorption, reduced local irritation and elimination of unwanted intestinal retention of polymeric material, when compared to non-disintegrating single unit dosage form., Micro beads are small, solid and free flowing particulate carriers containing dispersed drug particles either in solution or crystalline form that allow a sustained release or multiple release profiles of treatment with various active agents without major side effects.[1]

Clonidine Hydrochloride a centrally acting sympatholytic and Imidazoline-derivative hypotensive agent; selective α2-adrenergic agonist. It stimulates alpha2-adrenergic receptors in the brainstem to decrease sympathetic nervous system outflow.[2] It is also administered epidurally to treat pain. It is prescribed alone or in combination for the reduction of high blood pressure and is an adjunct for the treatment of cancer pain when pain persists during intraspinal opiate treatments.[3] It act by stimulating alpha-adrenergic receptors in CNS, decreasing sympathetic outflow, inhibiting vasoconstriction, and ultimately reducing blood pressure. Also prevents transmission of pain impulses by inhibiting pain pathway signals in brain.[4]

The objective of the work was to design multiple unit dosage form as microbeads of a drug meant for management of anxiety and hypertensive disorder. Microbeads offers numerous advantages for releasing one of the drugs or part of the same drug immediately while remaining drug or parts of the same can be sustained release. These are useful where drug-excipients and drug-drug interactions are predictable with single type dosage form.

MATERIAL AND METHOD:

Material:

Clonidine was received as a gift sample from Kalindi Medicure Pvt. Ltd, Vapi (India). Sodium alginate (Himedia chemicals, Mumbai), Calcium chloride (Unichem chemicals, Mumbai), HPMC and chitosan (SD. Fine chemicals, Mumbai).

Methods:

Preparation of Clonidine loaded micro beads:

A solution of sodium alginate was prepared in 100ml of de-ionized water. In 50ml of sodium alginate solution, 200 mg of Clonidine was dispersed uniformly. Bubble free dispersion was dropped through a syringe with a needle into 100ml aqueous calcium chloride solution and stirred 500rpm. After stirring for 30minutes, the mirobeads were separated by filtration, washed with distilled water and finely dried at 700C for 6h in an oven.

Table 1. Composition used formulations

Formulation code	Sodium Alginate % (w/v)	Calcium Chloride % (w/v)	HPMC % (w/v)	Chitosan % (w/v)
F1	2	1.25	0.5	0
F2	2	2.5	1	0.5
F3	2	5	1.5	1
F4	2	1.25	0.5	0
F5	2	2.5	1	1
F6	2	5	1.5	1.5

Particle size determination

The diameter of microbeads was found using an optical microscope as well as polarized light near about 50-100 microbeads were examined and average diameter was calculated using ocular micrometer**.**

Determination of Bulk Density

It is ratio of weight by volume. It was resolute by utilizing mark off cylinder, the precisely measured quantity of product microbeads inserted to cylinder and three times tapped. Noted the level, and calculated bulk density using formula[5].

$$\rho b = M/V$$

Where,

m = mass of sample,

v = volume of sample,

ρb =Density

Tapped Density

The sample of about 10 cm3 of powder was carefully introduced in 25 ml glass cylinder. The cylinder tapped at 1 inch height, with intervals of 2-3 second on a rough wood surface three-four times. Density of Bulkiness calculated by using equation

$$Do = M / Vp$$

Here,

Do = Tap density

M = samples wt (gm)

Vp = final material volumes (cm^3)

Angle of repose

It was carried out, using funnel, at sufficient height funnel was fixed and, microcapsules were added through it until the pile touched at bottom of funnel. Pile height as well as radius measured and using formula angle of repose calculated[5,6].

$$\tan \theta = h/r$$

Here,

r = height

r = is radius of pile

Percentage yield

It was determined by weighing after drying. The précised mass of produced microbeads were divided with mass of total non–volatile components utilized for the microbeads preparation, which gave the total percentage yield of microbeads [7].

$$\% \text{ Yield} = \frac{\text{Actual weight of product} \times 100}{\text{Total weight of excipients and drug}}$$

Drug Entrapment Efficiency (DEE)

From accurately weighted samples of prepared microbeads was extracted into buffer pH 7.4. Then extracts diluted using buffer solution (pH – 7.4). Resultant extract analysed for Clonidine hydrochloride sphectrophotometricaly at 313nm.

The drug content was calculated from standard curve.

$$\% \text{ Drug entrapment} = \frac{\text{Calculated drug concentration}}{\text{Theoretical drug concentration}} \times 100$$

In-vitro drug release profile of formulated microbeads

The dissolution studies executed utilizing (type II) XXIV USP dissolution rate test apparatus in 0.1 N HCl for 2 hrs followed by pH 7.4 900ml dissolution media, at 50 rpm and 37 ± 1^0C temperature upto 12 hrs. using ELICO – 164 U.V. Spectrophotometer double beam, 5ml of samples taken at different time gaps and 5ml of same dissolution medium added to uphold sink condition. Withdrawn aliquots diluted and analyzed spectrophotometrically at 313nm. The percent release of Clonidine Hcl calculated and graph plotted against time [8].

Drug Release Kinetic Studies

The drug dissolution data were subjected to release kinetic studies to find out means of drug release from the prepared microbeads[9].

Accelerated Stability Studies of the optimized batch

The microbeads from the selected and optimized batch were studied for stability and kept under the accelerated conditions of temperature and moisture (humidity) for the period of six months. This microbeads stability was studied at Temperature 40°C and Humidity 75% RH conditions. Every sample separately weighed and enclosed by aluminum foils and sealed in black PVC bottle and kept in specified conditions at humidity chamber for six months. The formulation was checked for physical changes also analyzed for dissolution study [10].

Morphological Study using SEM

Microcapsules mounted directly on scotch double adhesive tape analyzed under scanning electron microscope SEM model XL-30, operated at 15K SEM thickness of 100% using FEI-Philips Analytical Electron microscope (Diya labs,Mumbai) [9].

RESULT AND DISCUSSION:

Micromeritics Studies:

The results of the density of bulkiness and density of tapping were mentioned in table. Bulkiness values were lies in 0.297 to 0.542 g/cm3 and density of tapping values lies in 0.508 to 0.654 g/cm3 i.e. less than 1.2, indicates good packing. The values of Average particle size and angle of repose were lies in between 291.46 ±8.3 to 432.62 ±7.3, and 250-12' to 300-20', respectively indicates acceptable particle size, flow property and also good packing ability.

Table 2. Micromeritics Studies of Microbeads

Batch	Avg microbead size	Bulk Density	Tap Density	Angle of Repose
F1	291.46±8.3	0.298	0.522	250-15'
F2	323.44±6.9	0.542	0.654	260 -20'
F3	356.88±8.6	0.526	0.636	250-12'
F4	263.84±8.3	0.430	0.508	300-20'
F5	327.65±7.5	0.482	0.528	250-06'
F6	356.22±8.1	0.516	0.616	310-24'

Percentage recovery (i.e. Yield) of microbeads

Best % recovery was obtained for batch F6 - 96.47 %. Overall o% recovery of microbeads obtained > 82%.

Estimation of Clonidine HCl.

Formulation F6 gave well >84 % drug content. This batch gave 92.30 %, other formulations gave little bit drug loading than this batch. It can be happened due to viscosity caused by used material.

Table 3. Percentage yield and Percent drug entrapment of microbeads

Batch	% yield	%Drug Entrapment
F1	84.14±0.9	82.92±1.4
F2	86.40±3.6	85.12±2.4
F3	90.25±1.9	86.30±1.1
F4	82.62±2.6	86.48±2.6
F5	82.71±1.4	85.94±1.5
F6	83.50±1.7	86.46±2.6

*All the values represent mean ± standard deviation (n=3)

***In-vitro* Release Profile Study of Formulated microbeads**

Table 4. In vitro Cumulative %drug release profile

S.no	Time	% drug release					
		F1	F2	F3	F4	F5	F6
1	0	0	0	0	0	0	0
2	1	7.137	8.517	7.594	8.450	6.472	7.650
3	2	12.982	13.271	13.160	13.748	13.532	13.872
4	3	22.874	24.482	25.654	25.759	25.593	24.981
4	4	38.764	37.268	38.147	37.620	38.398	39.760
5	6	62.765	61.734	62.157	65.650	63.564	62.705
6	8	82.726	84.372	85.245	83.746	84.650	85.760
7	10	98.659	98.360	98.590	97.540	98.380	97.853

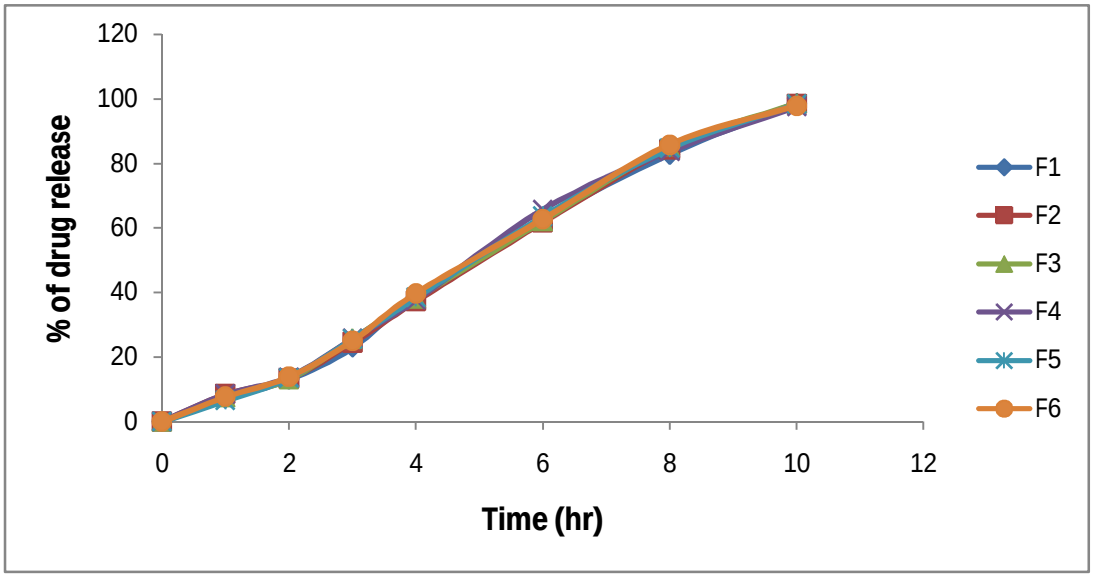
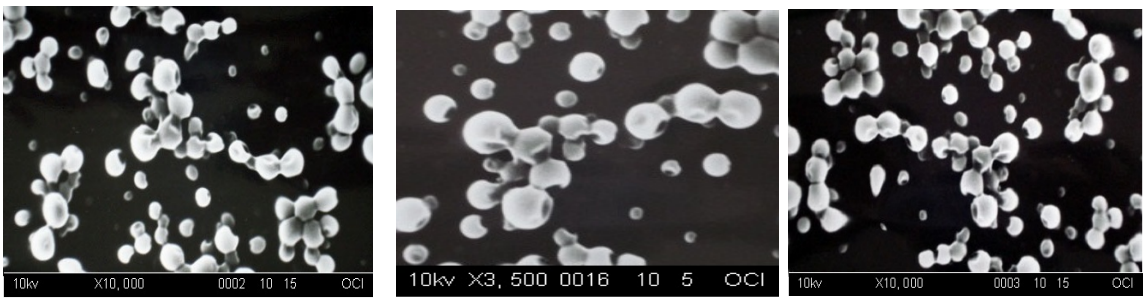


Fig 1. In-vitro Release Study of Formulated Microbeads of Clonidine

The results demonstrated that formulations (F1, F2, F3) showed Clonidine discharge speed in series of 91-94% when compared (F4, F5 and F6) demonstrated a Clonidine discharge speed from 86. -93% up to duration of 12 hours. This denotes that if quantity of rate retarding polymer raised, leads to retard discharge of drug. The synergistic effect was observed when the HPMC was combined with xanthan gum. Hence batch F1 indicates the better results than other prepared batchs. As formulation F6 shown 97.78% cumulative drug release pattern, this was according to the Acceptance Table of Test 2 given in USP-NF 2007 time duration of 12 hrs. When the HPMC combined with the natural gums is used for retarding drug discharge. Process of Clonidine HCL liberate from matrix involve solvent diffusion in to the matrix, polymer gelation, solubilization Clonidine HCL and drug transfer along eddies of medium.

Morphological Study using SEM (F6)



(A) (B) (C)

Fig. 2: shape and size of the beads (F6)

Drug Release Kinetic Studies

The drug dissolution data was checked to discharge kinetics to check basis for medicament release by microbeads-

***KMP = KorsmeyerPeppas model *HXC = Hixson Crowell model**

The batch F6 followed the zero order and non Fickian drug release except batch F3, it follows the Hixson crowel model non fickian drug release.

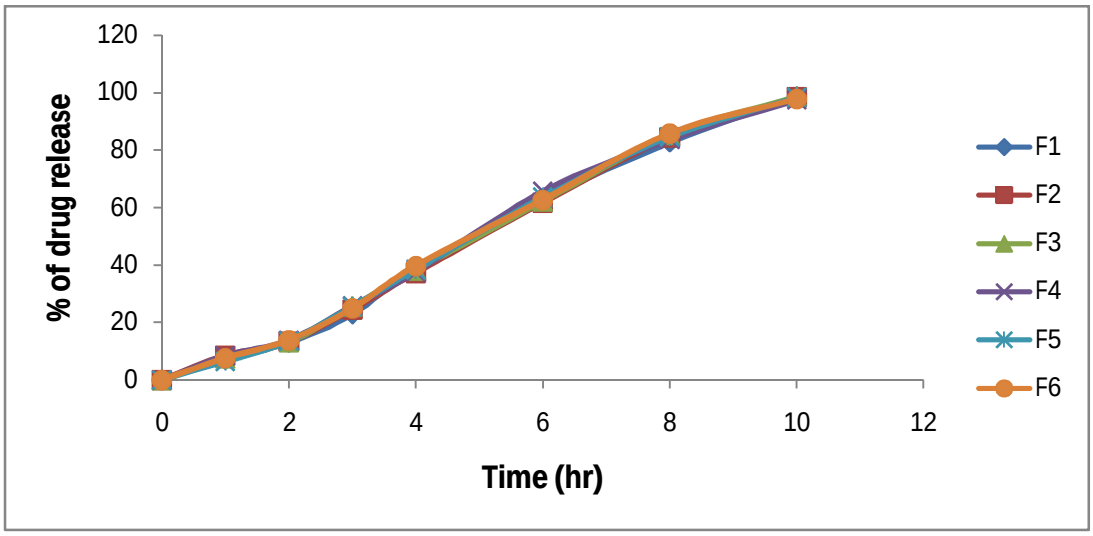


Fig. 3. Zero order release kinetic of microbeads

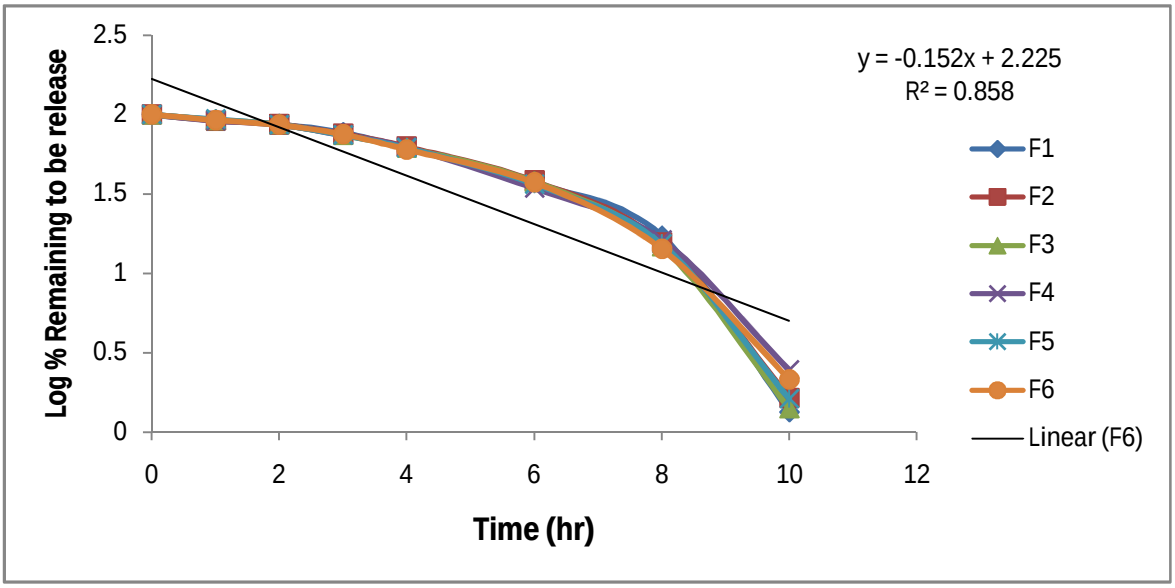


Fig 4: First order Release Kinetics

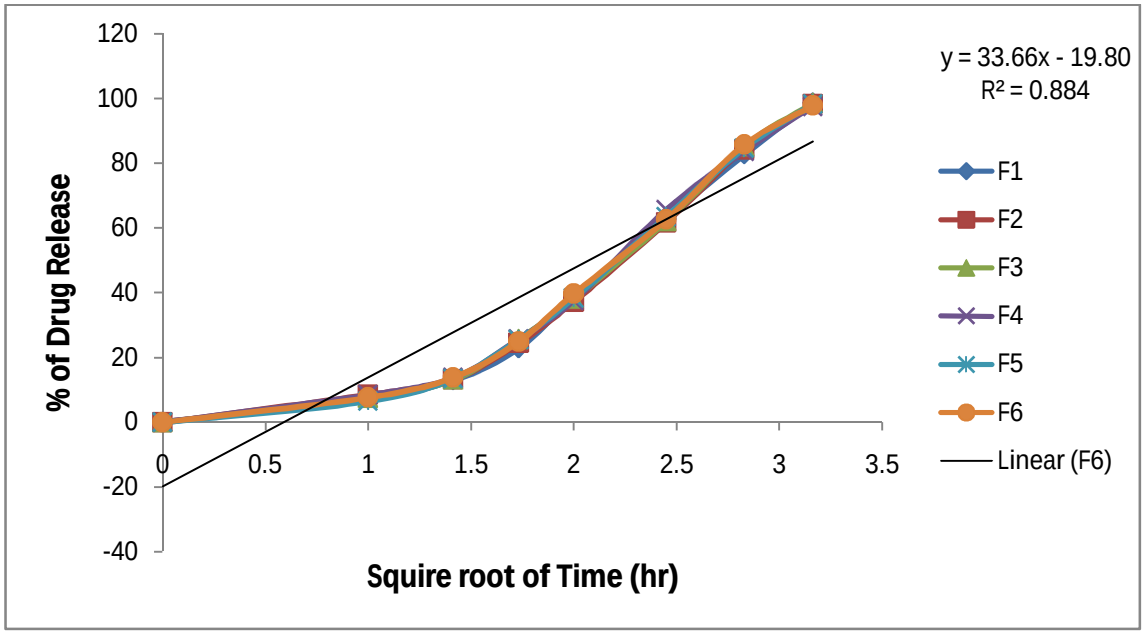


Fig 5: Higuchi Equation of Micro beads

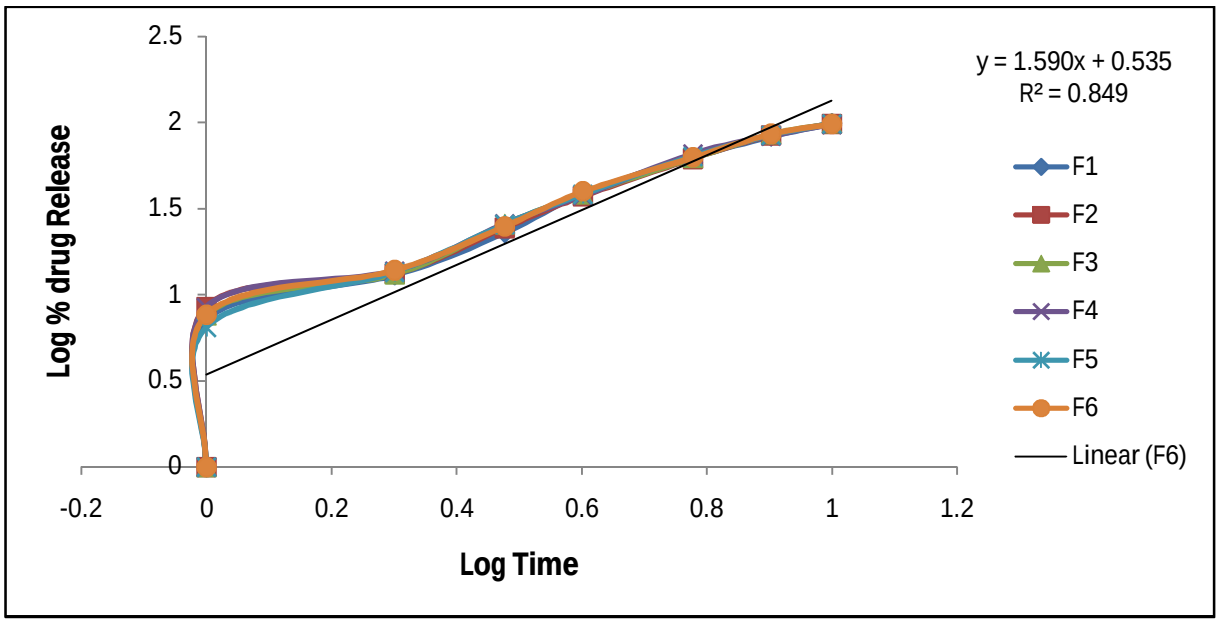


Fig 6: Pappas Equation of micro beads

Accelerated Stability Studies

The microbeads from the selected and optimized batch (FH) were studied for stability and kept under the accelerated conditions like raised temperature and moisture up to period of six months. The results revealed no marked alterations in physical appearance and drug releasing properties.

Table 5. Accelerated stability testing effect of temperature and humidity on *in-vitro* drug release for formulation F6

Time (Hours)	Cumulative % Drug Released			
	At 0 Month	At 2nd Month	At 4th Month	At 6th Month
0	0	0	0	0
1	20.96	19.69	19.19	18.89
2	27.47	25.87	24.17	23.97
3	33.63	31.83	30.93	30.13
4	42.72	41.12	40.92	40.32
5	54.19	52.87	52.17	51.97
6	61.15	60.13	59.83	59.23
7	73.81	71.89	71.21	70.11
8	82.72	81.26	80.86	80.21
9	88.63	86.93	86.13	85.33
10	90.94	88.24	87.94	87.14
11	94.49	93.94	93.14	92.64
12	97.78	95.81	95.12	94.82

Conclusion:

Clonidine hydrochloride are given into conventional, immediate releasing preparations, the frequency of administration increased up to twise-thrise time for one day because of shorter biological half life.

In such a case, the sustained release formulation will be beneficial than the immediate release dosage form as therapeutic level is maintained for an extended period of time, eliminating maxima in drug concentration commonly associated with multiple doses.

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