Research Article
CODEN (USA): IJPLCP

ISSN: 0976-7126
Thakur & Ghatuary, 12(12):1-9, 2021

International Journal of Pharmacy & Life Sciences
Open Access to Researcher

Formulation of Modified Release Matrix Tablets of Salbutamol Sulphate Using Accelerating Agents

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Article info

Received: 09/11/2021

Revised: 17/11/2021

Accepted: 26/12/2021

www.ijplsjournal.com

Abstract

The present study was focused to develop and evaluate the matrix tablets of salbutamol containing cellulose derivative and natural gums as release modifying polymer. In vitro release studies showed that formulation F-8 which contained Xanthan gum: Guar gum: HPMC (2:1:3) was chosen as optimized formulation because it can sustained release till 8 hours to release 96.84±1.57 percent of drug.

Key-words: Matrix Tablet, Accelators, Evaluation

Introduction

For many years, one of the major axes in pharmaceuticals research was the synthesis of new active ingredients capable of delivering therapeutic improvement. This sustained release dosage form is mainly designed for maintaining therapeutic blood or tissue levels of drug for extended period of time with minimized local or systemic adverse effects. This is accomplished by attempting to obtain Zero order release from the designed dosage form. Zero order release constitutes drug release from the dosage form that is independent of the amount of drug in the delivery system at a constant release rate. Systems that are designed for prolonged release can also be attributed as achieving sustained release delivery systems. Repeat action tablets are an alternative method of sustained release in which multiple doses of drugs are contained within a dosage form and each dose is released at a periodic interval, while delayed release systems may not be sustaining, since often the function of these dosage forms is to maintain the drug within the dosage form. Overall, administration of sustained released dosage forms enables increased reliability of therapy. The basic rationale for controlled drug delivery is to alter the pharmacokinetics and pharmacodynamics of therapeutically active moieties by using either polymer or modifying parameters inherent in a selected route of administration. [1-2]

In conventional oral dosage forms, which include capsules, solutions, suspensions and tablets, the drug is released by dissolution or diffusion. The resulting pattern of drug concentration in plasma can vary widely and may cause inconsistent and undesired clinical effects. The high peak blood concentration reached soon after administration may result in adverse effects.

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ISSN: 0976-7126
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With controlled release products the precise rate, extent or timing of drug entry into the blood stream is predetermined or achieved with an integral drug specific composition, structure or mechanism. [3-4]

Salbutamol is a white or almost white, crystalline powder. Freely soluble in water; slightly soluble in ethanol (95%) and in ether; very slightly soluble in dichloromethane. Salbutamol or albuterol, a moderately selective beta(2)receptor, is widely used as a bronchodilator to manage asthma and other chronic obstructive airway diseases. The R-isomer, levalbuterol, is responsible for bronchodilation while the S-isomer increases bronchial reactivity. The R-enantiomer is sold in its pure form as levalbuterol. As salbutamol is a beta (2) adrenergic agonist it stimulates beta (2) adrenergic receptors. It's binding to beta (2) receptors in the lungs results in relaxation of bronchial smooth muscles. It is believed that salbutamol increases cAMP production by activating adenylate cyclase, and the actions of salbutamol are mediated by cAMP. [5]

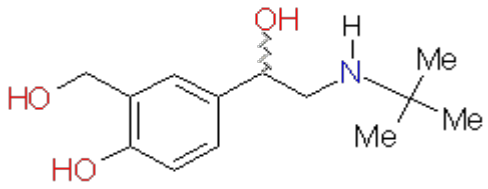

Figure: 3.1 Structure of Salbutamol

Material and Methods

Preformulation studies

Preformulation studies were performed using standard procedure.

Formulae design

The formula proposed for salbutamol sulphate involved the principle of matrix tablets. The formulation variables were polymer: drug ratio.

Table 1 F-1: Formulation of matrix tablet with HPMC only

Sr.No.	Ingredients	Amount for 1 tablet	Amount for 200 tablets
01	Salbutamol sulphate	8 mg	1.6 gm
02	HPMC	60 mg	12 gm
03	Mg. stearate	2 mg	0.4 gm
04	Talc	2 mg	0.4 gm
05	MCC	30 mg	6.0 gm

Table 2 F-2: Formulation of matrix tablet with guar gum only

Sr.No.	Ingredients	Amount for 1 tablet	Amount for 200 tablets
01	Salbutamol sulphate	8 mg	1.6 gm
02	Guar gum	60 mg	12 gm
03	Mg. stearate	2 mg	0.4 gm
04	Talc	2 mg	0.4 gm
05	MCC	30 mg	6.0 gm

Table 3 F-3: Formulation of matrix tablet with xanthan gum only

Sr.No.	Ingredients	Amount for 1 tablet	Amount for 200 tablets
01	Salbutamol sulphate	8 mg	1.6 gm
02	Xanthan gum	60 mg	12 gm
03	Mg. stearate	2 mg	0.4 gm
04	Talc	2 mg	0.4 gm
05	MCC	30 mg	6.0 gm

Table 4 F-4: Formulation of matrix tablet with guar gum and HPMC (1:1)

Sr.No.	Ingredients	Amount for 1 tablet	Amount for 200 tablets
01	Salbutamol sulphate	8 mg	1.6 gm
02	Guar gum	30 mg	6.0 gm
03	HPMC	30 mg	6.0 gm
04	Mg. stearate	2 mg	0.4 gm
05	Talc	2 mg	0.4 gm
06	MCC	30 mg	6.0 gm

Table 5 F-5: Formulation of matrix tablet with xanthan gum and HPMC (1:1)

Sr.No.	Ingredients	Amount for 1 tablet	Amount for 200 tablets
01	Salbutamol sulphate	8 mg	1.6 gm
02	Xanthan gum	30 mg	6.0 gm
03	HPMC	30 mg	6.0 gm
04	Mg. stearate	2 mg	0.4 gm
05	Talc	2 mg	0.4 gm
06	MCC	30 mg	6.0 gm

Table 6 F-6: Formulation of matrix tablet with xanthan gum and guar gum (1:1)

Sr.No.	Ingredients	Amount for 1 tablet	Amount for 200 tablets
01	Salbutamol sulphate	8 mg	1.6 gm
02	Xanthan gum	30 mg	6.0 gm
03	Guar gum	30 mg	6.0 gm
04	Mg. stearate	2 mg	0.4 gm
05	Talc	2 mg	0.4 gm
06	MCC	30 mg	6.0 gm

Table 7 F-7: Formulation of matrix tablet with xanthan gum, guar gum and HPMC (1:2:3)

Sr.No.	Ingredients	Amount for 1 tablet	Amount for 200 tablets
01	Salbutamol sulphate	8.0 mg	1.6 gm
02	Xanthan gum	10 mg	2.0 gm
03	Guar gum	20 mg	4.0 gm
04	HPMC	30 mg	6.0 gm
05	Mg. stearate	2.0 mg	0.4 gm
06	Talc	2.0 mg	0.4 gm
07	MCC	30 mg	6.0 gm

Table 8 F-8: Formulation of matrix tablet with xanthan gum, guar gum and HPMC (2:1:3)

Sr.No.	Ingredients	Amount for 1 tablet	Amount for 200 tablets
01	Salbutamol sulphate	8.0 mg	1.6 gm
02	Xanthan gum	20 mg	4.0 gm
03	Guar gum	10 mg	2.0 gm
04	HPMC	30 mg	6.0 gm
05	Mg. stearate	2.0 mg	0.4 gm
06	Talc	2.0 mg	0.4 gm
07	MCC	30 mg	6.0 gm

Table 9 F-9: Formulation of matrix tablet with xanthan gum, guar gum and HPMC (3:2:1)

Sr.No.	Ingredients	Amount for 1 tablet	Amount for 200 tablets
01	Salbutamol sulphate	8.0 mg	1.6 gm
02	Xanthan gum	30 mg	6.0 gm
03	Guar gum	20 mg	4.0 gm
04	HPMC	10 mg	2.0 gm
05	Mg. stearate	2.0 mg	0.4 gm
06	Talc	2.0 mg	0.4 gm
07	MCC	30 mg	6.0 gm

Table 10 F-10: Formulation of matrix tablet with xanthan gum, guar gum and HPMC (1:1:1)

Sr.No.	Ingredients	Amount for 1 tablet	Amount for 200 tablets
01	Salbutamol sulphate	8.0 mg	1.6 gm
02	Xanthan gum	20 mg	4.0 gm
03	Guar gum	20 mg	4.0 gm
04	HPMC	20 mg	4.0 gm
05	Mg. stearate	2.0 mg	0.4 gm
06	Talc	2.0 mg	0.4 gm
07	MCC	30 mg	6.0 gm

In the above formulae, xanthan gum and guar gum are the natural polymers and HPMC (Hydroxy propyl methyl cellulose) is a hydrophilic polymer, which are used to modify the drug release rate. Microcrystalline cellulose (MCC) is the most useful filler used for tablet formulations. It is water soluble and would modify the drug release for undergoing dissolution. MCC in aqueous solution plays a major role as important physical barrier, affecting the release kinetics, by reducing the tortuosity of diffusion pattern of the drug. Talc and magnesium stearate used as glidant and lubricant respectively.

Compression of blends to form matrix tablet

The compressed tablet is one of the most widely prescribed oral solid dosage forms in use today. Typically the ingredients which comprise the tablet blend include the active pharmaceutical ingredient (API) together with various excipients which not only act as carriers for the drug compound, but which also enhance its therapeutic effect, or efficacy. Three different techniques can be utilized for preparation of the mix prior to the compression stage: direct compression, dry granulation, or wet granulation. Direct compression is ideal for powders which can be mixed well and do not require further granulation steps prior to introduction to the tablet press.

Here we adopted dry granulation method; the lubricant was added to above mentioned different blends (F-1 to F-10) to improve the powder flow, so that the die of the tablet press fills accurately. Then all the tablets were punched with the help of manual single punch machine. [6-7]

Evaluation of tablet

All the prepared Sustained release tablets were evaluated for Hardness, Friability, Weight variation, Drug content and In-vitro dissolution. [6-7]

Results and Discussion

The present investigation was undertaken to formulate and evaluate salbutamol matrix tablet containing natural gums and cellulose derivatives for sustained release tablets. Preformulation study was done initially and results directed for the further course of formulation. The results of preformulation study of drug were reported in table 11-14.

Table 11: Organoleptic and physical properties of salbutamol sulphate

Test	Specification / limits	Observations
Color	White to off-white	White
Appearance	Crystalline powder	Crystalline powder

Table 12: Solubility profile of salbutamol sulphate in various solvents

Sr.No.	Solvent	Solubility	Inference
1.	Distilled water	++++	Freely soluble
2.	Ethanol	++	Slightly soluble
3	Ether	++	Slightly soluble
4	Dichloromethane	+	Very slightly soluble
5.	0.1 N HCL	+++	Soluble
6.	Phosphate buffer pH 6.8	+++	Soluble

Table 13: Melting point of salbutamol

Material	Specification	Observation
Salbutamol	157-158 ^{o}C (with decomposition)	158-160 ^{o}C

Table 14: Partition Coefficient values of drug

Sr. no.	Medium	Partition Coefficient (log P)
1.	n- Octanol : water	1.582

The different formulation of salbutamol sulphate matrix tablets was prepared by dry granulation technique. Tablets were compressed on a single punch hand operated tablet compression machine and randomly selected tablets were evaluated as per standard given in USP. Weight variation, hardness, friability, percent drug content tests were passed by all the tablets of formulation F-1 to F-10. The results summarized in Table 6.10.

The weight variation was determined by random selection of 20 tablets from each batch F-1 to F-10. According to USP 2002 the variation should be not more than 7.5% for tablets weighing less than 250 mg. Weight variation observed was because of the variation in flow property of different blends. But the results found to pass the limits.

Hardness test was conducted for all formulations as per the procedure given in materials and methods section. It is observed that the hardness was higher for formulations containing natural gum alone that is either xanthan gum or guar gum (F-2 or F-3). For all formulation from F-1 to F-10 the hardness was found in the acceptable range.

Table 15: Evaluation parameters for matrix tablets (n=3)

Formulation code	Evaluation parameters			
	Weight variation (%)	Hardness(mm)	Friability	Percent drug content
F1	1.960	4.4±0.65	0.55±0.085	100.74±2.2

F2	0.980	4.6±0.42	0.78±0.041	98.95±2.10
F3	2.941	5.0±0.70	0.77±0.039	102.29±2.87
F4	3.922	5.9±0.42	0.71±0.075	102.09±1.81
F5	0.857	4.8±0.94	0.66±0.066	100.63±2.12
F6	1.723	5.0±0.70	0.68±0.012	103.44±1.29
F7	3.932	4.3±0.86	0.65±0.034	98.17±0.48
F8	3.602	4.2±0.65	0.69±0.092	102.50±3.3
F9	2.694	4.3±0.86	0.73±0.064	97.49±1.31
F10	1.856	4.4±0.42	0.69±0.073	98.51±1.77

Friability test was conducted for formulation F-1 to F-10 as per the procedure mentioned in materials and methods. The friability loss was larger for F-1 because the HPMC is less efficient binder then gums. For other formulations F-2 to F-10 the loss due to friability was very lesser as the granules were bind by cohesive force of different polymers. The results passed the limits indicated in USP. Percent drug content uniformity was determined by procedure as per mentioned in materials and methods chapter. The percent drug content was determined to be ranged between 97.49-103.44%. Formulations from F-1 to F-10 passed the test as per USP.

Drug dissolution study was performed using USP apparatus I containing suitable media for dissolution. The detailed procedure followed was mentioned in chapter materials and methods. The dissolution was conducted for 8 hour and in the experiment it was observed that drug release was slow enough and polymer concentration was high enough to sustain the drug release. This is capable to avoid the dumping due to quick penetration of dissolution fluid in the tablet. Since we have selected HPMC, which is hydrophilic matrix agent. For hydrophilic polymer, the release should follow three steps. First is the penetration of the dissolution medium in the tablet matrix (hydration). Second, is the swelling with concomitant or subsequent dissolution or erosion of the matrix and third and final is the transport of the dissolved drug, either through the hydrated matrix or from the parts of the eroded tablet to the surrounding dissolution medium. The basic data of in vitro release of salbutamol sulphate for all the batches was analyzed statically.

Table 16: The cumulative percent drug release data of formulation F-1 to F-5

Time (min)	**Cumulative percent drug release**				
	F-1	**F-2**	**F-3**	**F-4**	**F-5**
0	0	0	0	0	0
30	28.05±4.56	33.33±1.15	24.60±1.52	26.66±1.52	22.33±2.08
60	47.76±0.59	43.66±1.52	45.60±1.15	48.35±1.54	45.67±0.54
90	55.66±0.64	51.82±2.64	53.68±0.57	59.37±2.51	51.01±0.57
120	69.82±0.72	67.87±1.20	63.68±0.55	68.71±2.53	68.33±2.19
180	77.07±0.63	73.67±5.45	75.09±0.77	72.07±1.73	71.03±1.22

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240	85.48±0.59	84.82±2.64	81.41±0.57	79.42±1.52	76.06±1.06
300	90.72±1.84	89.0±3.46	87.70±2.08	81.07±1.73	83.03±1.02
360	91.75±2.94	90.09±0.98	93.09±3.24	84.42±1.57	90.06±1.09
420	94.40±5.03	92.0±3.46	95.39±3.24	86.62±1.52	95.41±1.52

n=3, determinations

Graph 1: Cumulative drug release of F1 to F5

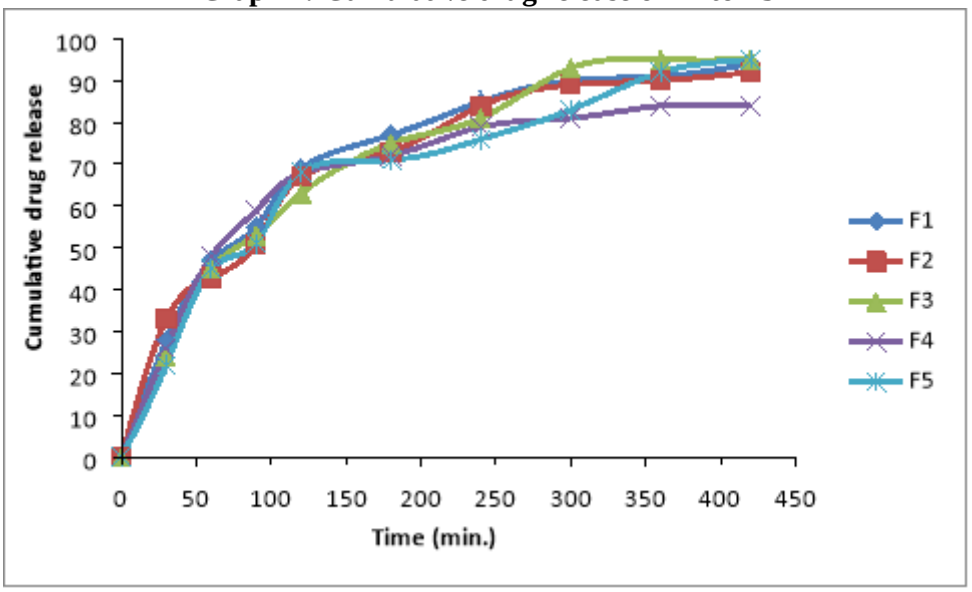

Table 17: The cumulative percent drug release data of formulation F-6 to F-10

Time (Min)	Cumulative percent drug release ± Standard deviation				
	F-6	F-7	F-8	F-9	F-10
0	0	0	0	0	0
30	19.66±1.52	11.66±1.55	12.66±1.53	10.33±1.86	16.94±1.38
60	37.38±2.08	26.35±1.43	24.35±1.52	24.35±1.25	30.45±1.76
90	66.40±1.92	43.03±2.87	40.03±2.01	41.37±1.86	45.34±2.94
120	72.73±1.83	58.71±2.18	52.71±1.15	52.38±1.35	56.30±1.04
180	82.74±1.17	71.65±1.22	64.39±1.22	56.72±1.53	64.48±1.49
240	87.42±1.28	84.63±0.57	73.73±0.57	61.72±1.52	77.26±0.86
300	90.09±2	89.24±1.52	88.73±1.08	66.06±1.38	83.58±1.68
360	91.19±2	92.40±2.08	95.40±2.86	71.73±1.95	92.48±2.37
420	94.09±2	94.14±1.05	96.84±1.57	89.35±1.38	96.48±2.37

n=3, determinations

ISSN: 0976-7126
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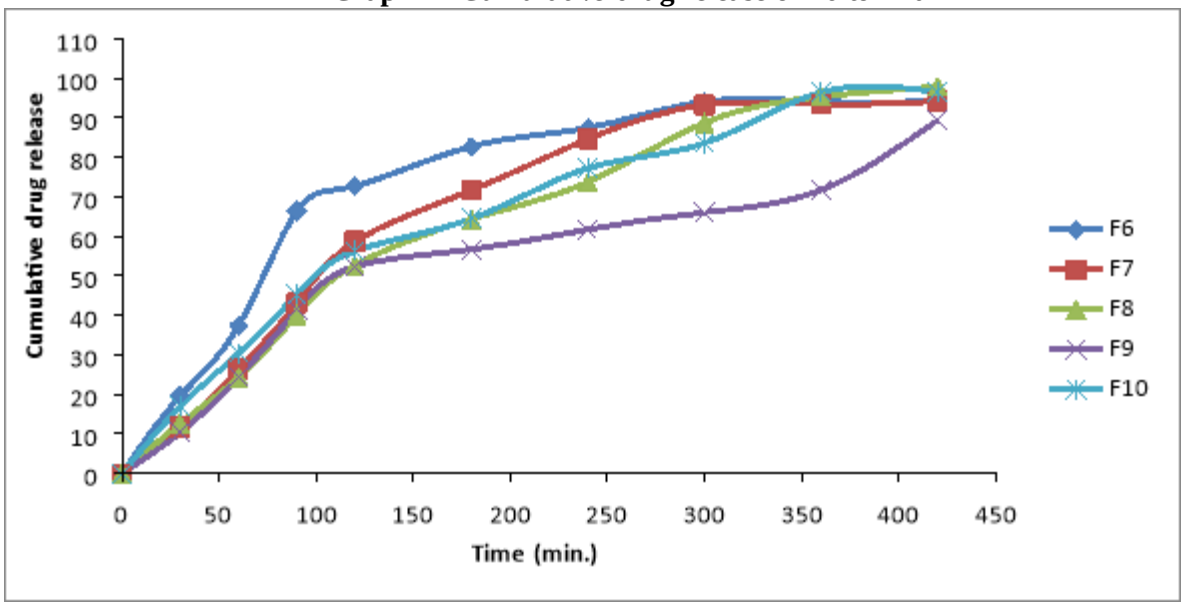
Graph 12 Cumulative drug release of F6 to F10



In this context the percent cumulative drug release was calculated which was characterized for maximum 8 hours where 90-100 % drug release occur. The cumulative percent drug release versus time plots of all the formulation show a sustained drug released pattern. By the comparison of cumulative percent drug release values it was observed that the formula F-8 may be selected as optimized formula. The cumulative percent drug release for rest of the formulations was lesser as compared to formulation F-8.

The reason for higher rate of drug release could be high aqueous solubility of drug and short diffusion path. Tablets of F-1, F-2 and F-3 batches containing only one polymer while formulation F-4 to F-10 containing more than one polymer for the extended release of the drug.

The formulation F-1 containing only one polymer HPMC therefore can sustain the drug release to 3 hour only. Guar gum alone (formulation F-2) can sustain drug release only for 2 hour; indicating guar gum alone is not sufficient to sustain drug release for a long duration. The formulation F-3 contain only xanthan gum, can sustain the release till 4 hour proving it is good matrix agent as compared to guar gum.

The formulations from F-4 to F-10 contains at least two polymer out of HPMC, Guar gum or/and Xanthan gum, therefore they sustained the drug release for a longer duration. The effect of polymer content was attributed to an increasing tortuosity and length of the diffusion path. For the formulations F-7 and F-9 the matrix tablet sustained drug release till 8 hour but they release drug not more than 95%; indicating that they are less efficient formulation. Formulation F-8 containing Xanthan gum, Guar gum and HPMC in the ratio 2:1:3, shows to sustain drug release till 8 hour and in 8 hour the cumulative percent drug release was 96.84. So, F-8 showed best results it was chosen as the optimized formula.

Further the optimized formula (F-8) and rest formulations were subjected for mathematical models to cross check the optimization and to explain the nature and mechanism of release from matrix tablets.

Conclusion

The formulation procedure is simple and does not involve lengthy procedures and use of several pharmaceutical excipients. Salbutamol sustained release matrix tablets were prepared successfully by direct compression method using HPMC and natural gums like xanthan gum and guar gum as polymers in different proportion, to retard the release and achieve required dissolution profile.

From the experimental results it can be concluded that,

- Guar gum when used as matrix polymer without any other polymer it modify very little drug release while either HPMC or Xanthan gum in combination or individually shows for significant effects on controlling the drug release.

The formulations prepared by combination of any two amongst selected polymer are found effective in controlling the drug release from the matrix.
When all the three polymers used in combination they exerts better control on drug release behavior, specially in a ratio 2:1:3 for Xanthan gum: Guar gum: HPMC respectively.
In vitro release studies showed that formulation F-8 which contained Xanthan gum: Guar gum: HPMC (2:1:3) was chosen as optimized formulation because it can sustained release till 8 hours to release 96.84±1.57 percent of drug.

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Cite this article as:
Thakur P. and Ghatuary S.K. (2021). Formulation of Modified Release Matrix Tablets of Salbutamol Sulphate Using Accelerating Agents. *Int. J. of Pharm. & Life Sci.*, 12(12):1-9.

Source of Support: Nil
Conflict of Interest: Not declared
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