

Effect of agar—gelatin compositions on the release of salbutamol tablets

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Abstract

The study was designed for the development of salbutamol-modified release tablet using various polymer composition of agar, gelatin A and gelatin B. The purpose is to observe the role of polymer composition on the modified dissolution rate of salbutamol. Pre-formulation trials were initiated by comprising different ratios of polymer blend in the tablets. Formulations were optimized based on their *in vitro* release performed in enzyme free simulated gastric fluid (0.1 N HCl, pH 1.2). Dissolution profiles of tablets were compared among the tablets made of agar, gelatin A, gelatin B and their blends agar-gelatin A, agar-gelatin B, gelatin A-gelatin B and agar-gelatin A-gelatin B in 1:1 ratio. Polymer compositions were fixed based on our desired sustaining activity of the tablet which showed a biphasic release profile with immediate release followed by sustained release. Polymer blends were more effective in controlling drug release. The better controlling behavior of polymer blends was explained by specific interaction between polymer components, their network structure and polymer–drug interaction.

Key words: Biopolymer blends, biphasic release, *in-vitro* release, simulated gastric fluid, specific interaction

INTRODUCTION

Polymer matrices are promising candidates in drug release controlling agents and are widely used in various dosage forms in pharmaceutical industry.^[1] Controlled or sustained release is advantageous as they provide desired activity and maintain desired therapeutic level of drug for prolonged period of time and reduce the number of doses, thus are emerging as better alternative over conventional immediate release medication. Varieties of natural polymers are being used effectively in various pharmaceutical products. These include proteins (gelatin), polysaccharides (chitosan, agar, acacia, agarose) and gummy exudates (guar gum, gum karaya). Agar is being used as sustained release agent in tablets, gels beads, microspheres and topical formulations,^[2-5] as swelling agent,^[6] viscosity

increasing agent in aqueous systems and as suspending agent^[7] in pharmaceutical suspensions but work on agar–gelatin blends tablets are scarce. Polymer blending give improved physical and mechanical properties due to their synergistic effect and thus are good candidates for controlled drug delivery systems. Here, we reported preparation of agar-gelatin blend tablets of salbutamol, a selective β_2 adrenoreceptor agonists, widely used for treatment of asthma^[8-12] which leads to the relaxation of bronchial smooth muscle and inhibits hyper sensitivity of mast cells. It is well absorbed following oral administration with peak plasma level occurring within 14 h (T_{max}). Though inhaled therapy is ideal for treatment of asthma as drug is directed directly to lungs thus increasing the efficacy of drug and also has minimal side effects but for very young, old and handicapped patients, unable to use inhaler, oral administration of drug is better alternative. Herein, the effect of various agar–gelatin compositions on the release of salbutamol is discussed.

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MATERIALS AND METHODS

Agar was a gift from Central Salt and Marine Research Institute, Bhavnagar, Gujrat. It has been extracted from the red seaweed *Gracilaria dura* collected from the Gulf of Mannar at the southeast coast of India, employing a patented method.^[13] Gelatin type A (from porcine skin, bloom number 175) and type B (from bovine skin, bloom number 225) gelatin were purchased from Sigma-Aldrich and used as received. The two types of gelatins are characterized by their mode of manufacture. Type A gelatin

(pH 3.8–6.0; isoelectric point 6–8) is derived by acidic hydrolysis of pork skin and contributes plasticity and elasticity to the blend. Type B gelatin (pH 5.0–7.4; isoelectric point 4.7–5.3) is derived by basic hydrolysis of bones and animal skin and contributes high gel strength to the blend. Gelatin used in the pharmaceutical industries is a blend of these two types, although sometimes only Type A or Type B is used. Salbutamol was a generous gift from Department of Pharmaceutics, Jamia Hamdard University, New Delhi.

Formulation of modified release tablets

Tablets were prepared by wet granulation technique using agar and gelatin in combination and these polymers were used as binder in the form of aqueous homogenous slurry. Pre-formulation studies had shown that agar used in dry powder form is not much effective as release retarding agent and more amounts is required to get the same effect as lesser amount of slurry is used. Slurry of agar was prepared by allowing it to swell completely in 100 ml of warm water by stirring continuously using mechanical stirrer for 2 h. Salbutamol and magnesium oxide (light) were passed through 40# mesh and mixed homogeneously using polybag. The blend was then granulated with binding agent, which was prepared. The granules were heated at 60°C till the moisture content attains 1.2%, passed through 20# and were blended uniformly with 60# passed magnesium stearate and aerosil. Granules were compressed into tablets at the weight of 150 mg per tablet using 6 mm, plain round biconcave standard punches and die in clut rotary tablet compression machine. Hardness of the tablets was adjusted to 6 kg/cm² using Monsanto hardness tester. Thicknesses of all tablets were found to be 4.59 ± 0.48 mm using vernier callipers. Friability of all batches was observed to be less than 1%. Formulation of salbutamol tablets is given in Table 1.

Details of polymer blend matrices

Polymers [Table 2] were incorporated by mixing agar with

two types of gelatin; Type A (acid processed), Type B (alkali processed), their mixture Type AB in 1:1 ratio (w/w) and also using Gelatin AB (1:1) alone.

In vitro dissolution studies

Release experiments were performed in dissolution apparatus II (VEEGO Model VDA-8DR) as a function of time for 8 h. Dissolution medium was enzyme free 0.1 N HCl (900 ml) maintained at 37 ± 0.5 °C. Tablets were tested in triplicate for each batch with paddle speed of 50 rpm. Three millilitres of dissolution medium were taken at different time intervals, filtered through 0.4 µm sterile filters and analyzed spectrophotometrically (UV-1601 of Shimadzu) at 276.4 nm. An equal volume of the same release medium (same temperature) was supplemented to keep volume constant.

Analysis of release profile

Dissolution profiles were analyzed using model dependent and model independent methods.^[14]

Model dependent analysis

Various mathematical models had been used extensively for comparison of the dissolution data.^[15] Apart from comparison, modeling also provides insight into the mechanism of drug release. These were enlisted in Table 3 along with their characteristic release mechanism.

Model-independent analysis

Model independent analysis directly compares the dissolution data by converting the whole profile or profile differences into a single value. These include both ratio-test and pair-wise procedures. Ratio-tests are parameters $t_{x\%}$ and sampling time, Moment of dissolution profile (MDT) and dissolution efficiency DE%.^[16] The $t_{x\%}$ corresponds to the time necessary to the release of a determined percentage of the drug (e.g., $t_{20\%}$, $t_{50\%}$, $t_{80\%}$) and sampling time corresponds to the amount of drug dissolved

Table 1: Formulation of salbutamol tablets

Excipients	Quantity (mg/tab)
Salbutamol	9.6
MgO (light)	126.4
Polymer	12.0
Mg stearate	1.0
Aerosil	1.0
Water	Q.S

Table 2: Composition of agar-gelatin and gelatin-gelatin blend matrices

Polymer blends	Formulation code	Ratio
Agar + gelatinA	AgarGelA	1:1
Agar + gelatinB	AgarGelB	1:1
Agar + gelatinAB	AgarGelAB	1:1
Gelatin A + gelatinB	GelAB	1:1

Table 3: Various mathematical models with drug release mechanism

Release models	Equation	Release mechanism
Zero order	% diss = kt	Constant release rate
Higuchi	% diss = $kt^{0.5}$	Fickian diffusion mechanism
Korsmeyer–Peppas	% diss = kt^n	Diffusion- based mechanisms
Peppas-Sahlin	% diss = $kt^m + kt^{2m}$	Diffusion+relaxation-based mechanism
Hixson–Crowell	% diss = $100 [1-(1-kt)^3]$	Erosion-release mechanism
First order	% diss = $100(1-\exp(-kt))$	First-order mass balance
Weibull	% diss = $100(1-\exp(-t/T_0)^\beta)$	Life-time distribution
Logistic	$100 \left[\frac{\exp(\alpha + \beta \log t)}{1 + \exp(\alpha + \beta \log t)} \right]$	S-shaped model

in that time (e.g., $t_{20\text{min}}$, $t_{50\text{min}}$, $t_{80\text{min}}$). First two parameters are frequently used by Pharmacopeias as an acceptance limit of the dissolution test (e.g., $t_{45\text{min}} \geq 80\%$). Dissolution efficiency values are parameter useful for the evaluation of *in-vitro* dissolution. It is defined as the area under the dissolution curve up to a certain time expressed as percentage of the area of the rectangle expressed by 100% dissolution in the same time. It is given by

$$DE \% = \frac{\int_{t_1}^{t_2} y dt}{y_{100}(t_2 - t_1)} \times 100 \quad (1)$$

Pair-wise procedures are fit factors (difference factor f_1 and similarity factor f_2) recently proposed by Moore.^[17] Fit factors were adopted by FDA Center for Drug Evaluation and Research (CDER) and similarity factor was adopted by the European Medicines Evaluation Agency (EMA) as an assessment criterion of similarity between two *in-vitro* dissolution profiles.^[18] The fit factors compare the difference and similarity between the percent drugs dissolved per unit time for a test and reference product. In our study these fit factors were chosen to compare the dissolution profiles. The difference factor f_1 is proportional to the average difference between the two profiles, whereas similarity factor f_2 is inversely proportional to the log of average squared difference between two profiles. These are represented as

$$f_1 = \left\{ \frac{\sum_{t=1}^n (R_t - T_t)}{\sum_{t=1}^n R_t} \right\} * 100 \quad (2)$$

$$f_2 = 50 \log \left\{ \left(1 + \frac{1}{n} \sum_{t=1}^n (R_t - T_t)^2 \right)^{-0.5} \right\} \times 100 \quad (3)$$

where n is the number of dissolution sample times and R_t and T_t are the individual or mean percent dissolved at each time point, t , for the reference and test dissolution profiles, respectively. According to FDA guidelines for two profiles to be considered similar f_1 and f_2 values should be close to 0 and 100, respectively. Generally, f_1 values up to 15 (0–15) and f_2 values >50 (50–100) are acceptable. Shah et al.^[19] recommended that because of the sensitivity of these factors to the measurements after 85% dissolution, the number of sample points be limited to not more than one, once any test product reaches 85% dissolution.

RESULTS

Dissolution profile of various tablets

Dissolution profiles of pure agar, pure gelatin A and B and of various blends, i.e., AgarGelA, AgarGelB, AgarGelAB, and GelAB along with their components are presented in Figures 1-5. The standard deviation (SD) of release percentage between different batches of same components was in the range

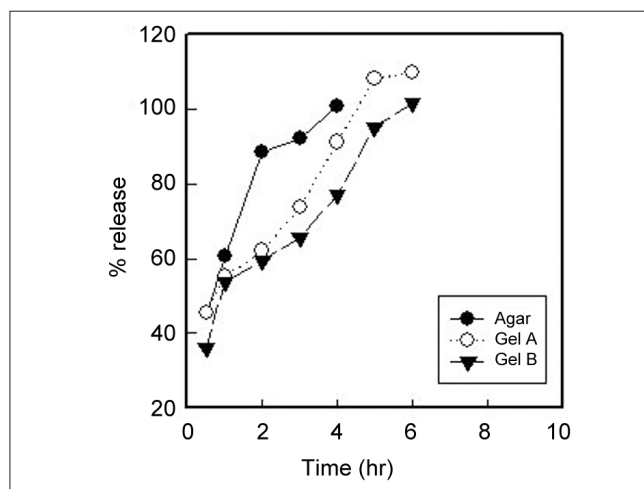


Figure 1: Dissolution profiles of salbutamol from tablet made of pure agar, gelatin A, and gelatin B

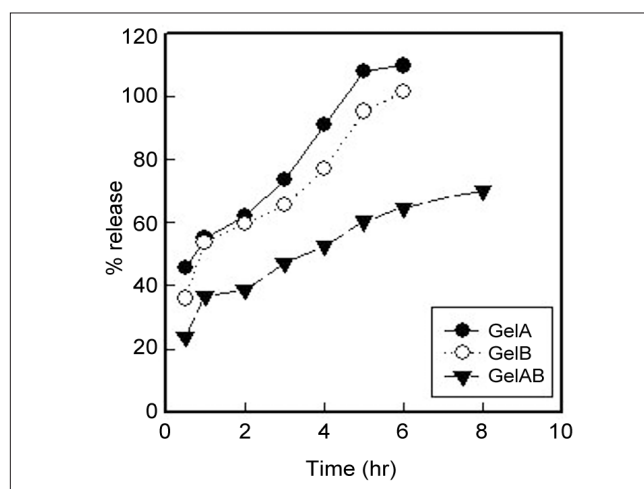


Figure 2: Dissolution profiles of salbutamol from tablet made of pure gelatin A, gelatin B and their mixture gelatin AB (1:1)

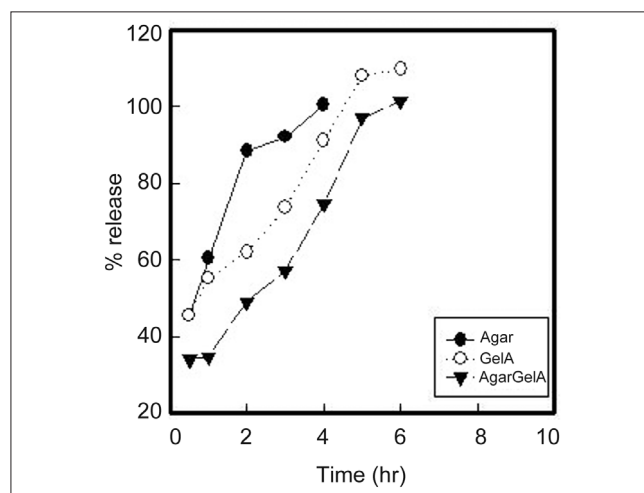


Figure 3: Dissolution profiles of salbutamol from tablet made of agar, gelatin A, and agar-gelatin A (1:1)

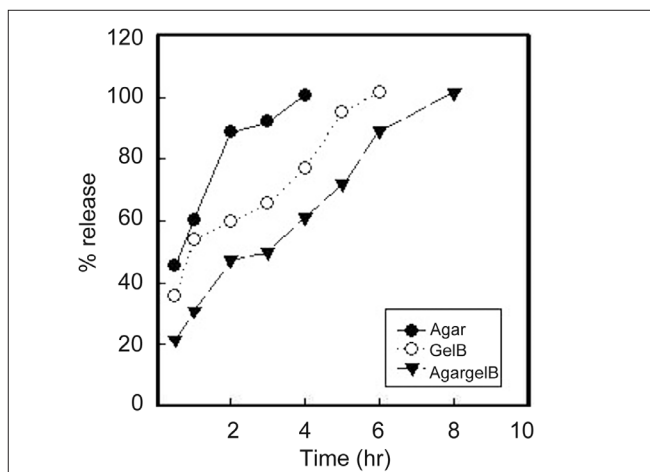


Figure 4: Dissolution profiles of salbutamol from tablet made of agar, gelatin B, and agar-gelatinB (1:1)

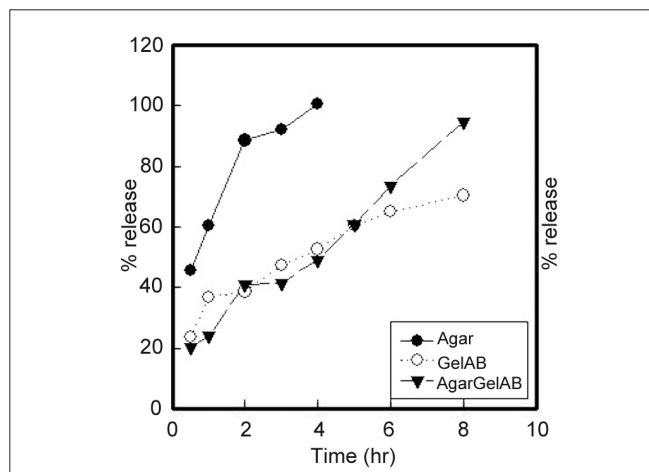


Figure 5: Dissolution profiles of salbutamol from tablet made of agar, gelatin AB, and agar-gelatin AB (1:1)

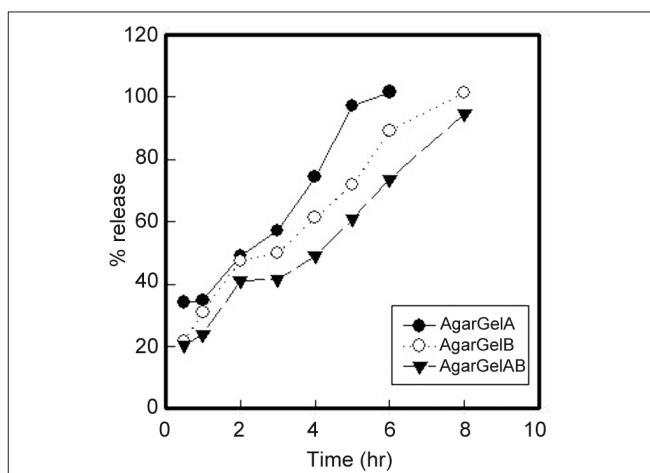


Figure 6: Dissolution profiles of salbutamol from tablet made of agar-gelatin A and B, and agar-gelatin AB (1:1)

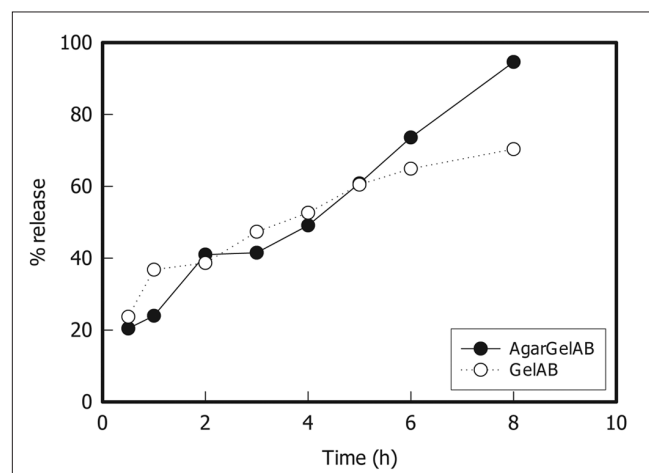


Figure 7: Comparison of dissolution profiles of salbutamol from best selected formulations made of agar-gelatin AB, and gelatin AB (1:1)

0.002-0.01. Comparison of drug release percentage from tablets made of different pure components and their blends showed trends in the order Agar>GelA>GelB, Agar>GelA>AgarGela, Agar>GelB>AgarGelB, Agar>GelAB≈AgarGelAB and GelA>GelB>GelAB, respectively.

DISCUSSION

It was seen [Figures 1-4] that polymer blend matrices were better release controlling agents than pure agar or gelatin. Drug release from polymer matrices depends upon various factors, viz. drug solubility, polymer type, polymer–polymer interaction, polymer–drug interaction. Our results could be well explained by taking into account specific interaction between agar and two gelatins. Agar is a polysaccharide having numerous OH groups at pH 7.5. Gelatin is a polyampholyte with amine and carboxyl functional groups. Gelatin A is positively charged in aqueous solution due to protonation of amino groups (NH_3^+) while Gelatin B is negatively charged

due to deprotonation of carboxyl groups (COO^-). These COOH groups interact with OH groups of Agar in AgarGelB forming covalent ester bond ($-\text{COO}$) with removal of water. In case of AgarGelA there is H-bonding between NH_2 and OH groups. In AgarGelAB system, three interactions compete with each other, H-bonding, ester bond formation ($-\text{COO}$), and peptide bond formation ($-\text{NH}-\text{CO}-$) between NH_2 groups of GelA and COOH groups of GelB. All these interactions can take place selectively or simultaneously. Therefore, the microstructure of AgarGelAB was the strongest to hold the drug for long time and release it slowly. In the case of AgarGelA system, the amino group of gelatin A selectively forms hydrogen bonds with hydroxyl groups of agar generating a gel which is not strong enough compared to other blend matrices. Similarly interaction between gelatin A and gelatin B in GelAB tablets are both H-bonding and between COOH and OH groups giving rise to complex and stronger network. Presence of three OH groups and one NH group in salbutamol may lead to same type of interaction with functional groups of agar, gelatin or both. A comparison of release profiles of all four

Table 4: Dissolution efficiency data

	$t_{x\%}$			Sampling time		Dissolution efficiency	
	AgarGelAB	GelAB		AgarGelAB %	GelAB %	AgarGelAB %	GelAB %
$t_{20\%}$	30 min	<30 min	t_{1h}	24	36		
$t_{50\%}$	4h	+ 3h	t_{4h}	49	62	40.4	35.8
$t_{80\%}$	>6h	< 6h	t_{8h}	95	90		

blends had shown [Figure 6] the decreasing trend in the order AgarGelA > AgarGelB > AgarGelAB \approx GelAB. Among all formulations GelAB and AgarGelAB [Figure 7] had been found to give better controlled release and were analyzed further using model dependent and model independent methods.

Model-dependent analysis

AgarGelAB tablets: Dissolution profile of AgarGelAB showed a biphasic drug release behavior, initial fast release up to two hours followed by a slow release. About 40% drug was released in the initial phase. Various mathematical models enlisted in Table 3 were applied to both phases to know the mechanism of drug release. Initial phase could be well fitted to Korsmeyer-Peppas equation with $R^2 = 0.97$ and exponent $n = 0.6$ describing a non-Fickian release. In non-Fickian drug release the relaxation time t_r (the time required for molecular rearrangement of polymeric chains is approximately equal to the characteristic time of diffusion t_d of the solvent (defined as the ratio of the solvent diffusion coefficient at the equilibrium and the square of a characteristic length), $t_r = t_d$). The second phase of drug release from 3rd hour onwards till 8th hour was best fitted with zero-order equation with release rate constant $k = 0.96$ mg/h. This phase was preceded by a very little drug release, 0.5%, from 2nd hour to 3rd hour.

GelAB tablets

These also showed a biphasic behavior but initial phase is up to 1 h releasing 36.8% of drug as compared to 23.9% from AgarGelAB. Second phase gave a good zero order fitting from 2nd hour onwards. Like AgarGelAB tablets, an intermediate release of about 1.8% was seen from 1st hour to 2nd hour followed by a zero order second phase release with release rate constant $k = 1.2$ mg/h.

Model-independent analysis

Dissolution efficiency in %, $t_{x\%}$ and sampling time are presented in Table 4.

Fit factors were calculated (using standard equations) between AgarGelAB and GelAB given which was $f_1 = 11.3$ and $f_2 = 52.5$. It could be seen that there was a good similarity between dissolution profiles of AgarGelAB and GelAB.

CONCLUSIONS

In-vitro dissolution profiles of tablets of all polymer types had shown that all Agar-gelatin blend matrix tablets had a better control on salbutamol release compared to tablets made of pure agar or pure gelatins. Agar-gelatin composition had marked effect on drug

release which was due to specific interaction/s between the polymers resulting into weaker or stronger structure. AgarGelAB and also GelAB were found to be best among all blend matrices showing modified release behavior which was biphasic, an initial fast release phase, followed by a slow release phase following zero order. Both phases were intermediated by an almost negligible release for 1 h. Such type of behavior is less known for polymeric matrices. This type of system is beneficial when immediate relief is required quickly and then a slow zero order release to maintain the therapeutic level.

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