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Original article

PREPARATION AND EVALUATION OF SODIUM ALGINATE POROUS DOSAGE FORM AS CARRIERS FOR LOW DOSED ACTIVE PHARMACEUTICAL INGREDIENTS

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Abstract

The present investigation was undertaken to fabricate porous controlled release dosage form of metoprolol tartarate using sodium alginate (SA) as a matrix forming agent and ammonium carbonate (AC) as a pore forming agent. This study evaluated a novel approach and newer technique for development of low dosed tablets by direct compression technique. Tablets were evaluated for pharmaco-technical properties and results were found to be satisfactory. Influence of pore forming agent on properties of tablets were mainly investigated. FTIR, DSC were conducted in order to show drug, polymer excipient compatibility. SEM studies were conducted in order to show the porous surface of tablets. Ammonium carbonate as a pore forming agent proves to be promising and was successful in creating pores on surface of tablets through which drug was loaded in tablets. SEM had given a clear picture showing major and minor pore with different pore size. Response Surface Curves (RSC) had been plotted in order to see the effect of pore forming agent on properties of tablets (disintegration, hardness and drug release). It was found that an increase in pore forming agent leads to decrease in hardness and disintegration time of porous tablets. Drug release was found to be drastically affected by concentration of pore forming agent present in respective batches of tablets. In-vitro release data shows that tablets follow zero order release mechanism which was further confirmed by Korsmeyer-Peppas, indicating that more than one mechanism for the drug release are involved, that is diffusion and erosion.

Key words: *Metoprolol tartarate, Pore forming agent, Porous tablets, Response surface curves.*

Düşük Dozlu Aktif Farmasötik Bileşenler İçin Taşıyıcılar Olarak Poröz Sodyum Aljinat Dozaj Formunun Hazırlanması ve Değerlendirilmesi

Bu çalışma, por oluşturucu bir ajan olarak amonyum karbonat (AC) ve matris oluşturucu bir ajan olarak sodyum aljinat (SA) kullanarak metoprolol tartaratın kontrollü salım yapan poröz dozaj formunun üretimi için yürütülmüştür. Çalışmada, doğrudan basım ile düşük dozlu tabletlerin geliştirilmesi için yeni bir teknik ve yeni bir yaklaşım değerlendirilmiştir. Sonuçlar farmako-teknik özellikler bakımından değerlendirilmiş ve sonuçların tatminkar olduğu bulunmuştur. Tabletlerin özellikleri üzerine por oluşturucu ajanın etkisi, başlıca araştırılan konu olmuştur. Etkin madde, polimer yardımcı madde geçimliliğini göstermek için FTIR ve DSC incelemeleri yapılmıştır. Tabletlerin poröz yüzeyini göstermek için SEM incelemesi yapılmıştır. Por oluşturucu bir ajan olarak amonyum karbonatın uygunluğu kanıtlanmış ve tabletlerin yüzeylerinde, içlerine etkin maddenin yüklendiği porların oluşturulmasında başarılı bulunmuştur. SEM, farklı çaplarda büyük ve küçük porları açıkça gösteren bir resim vermiştir. Por oluşturucu ajanın tabletlerin özellikleri (dağılma, sertlik ve etkin madde salımı) üzerine etkilerini göstermek için cevap yüzey eğrilerinin (RSC) grafikleri oluşturulmuştur. Por oluşturucu ajanın artışının poröz tabletlerin sertlik ve dağılma zamanlarında azalmaya neden olduğu bulunmuştur. Etkin madde salımının, tablet serilerinde içinde por oluşturucu ajanın konsantrasyonu ile çok belirgin derecede etkilendiği bulunmuştur. İn vitro salım verileri, etkin madde salımı için difüzyon ve erozyon gibi birden fazla mekanizmanın içerildiğini gösteren Korsmeyer–Peppas eşitliği ile de doğrulandığı gibi, tabletlerin sıfır derece salım mekanizmasına uyduğunu göstermiştir.

Anahtar kelimeler: *Metoprolol tartarat, Por oluşturucu ajan, Poröz tablet, Cevap yüzey eğrileri.*

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INTRODUCTION

Oral route has been the most popular and successfully used for sustained delivery of drugs because of convenience and ease of administration, greater flexibility in dosage form design and ease of production and low cost of such a system. The growing interest in controlled drug delivery release is because of its benefits like increased patient compliance due to reduced frequency of administration and less undesirable side effects. Microencapsulation of drugs in a hydrophobic matrix such as polymer, control the release of drugs. The term "control" includes phenomena such as protection and masking, reduced dissolution rate, facilitation of handling and spatial targeting of the active ingredient.

Research for alternative carriers has been increasing to suit for the industrial applications as well as to reduce the production cost and toxic effects. Recently, many natural polymers have been evaluated for their use in new drug delivery applications. The dissolution rate of drugs from the formulations containing viscous carriers is generally low due to the formation of gel layer on the hydrated surfaces, however, it is reported that the viscous ability of the carrier retards dissolution rate of highly water soluble drug (1).

Controlled release delivery systems provide a uniform concentration or amount of drug at absorption site and thus after absorption, allow maintenance of plasma concentration within a therapeutic range, which minimizes side effects and also reduces frequency of administration. These products typically provide benefits over immediate release formulations, including greater effectiveness, in the treatment of chronic conditions, reduced side effects, and greater patient convenience due to simplified dosing schedule (2,3).

Alginate is linear, naturally occurring polysaccharide extracted from brown sea algae. It contains D-mannuronic acid (M) and L-guluronic acid (G) acids which are arranged in homopolymeric MM or GG blocks separated by blocks with an altering sequence, MG blocks. In the presence of various divalent (Ca^{2+} and Zn^{2+}) or trivalent ions (Al^{3+}), an elastic gel is formed due to ionic interaction between the ions and carboxyl group, mainly of guluronic blocks (4). In recent years, pharmaceutical industries have shown profound interest in the use of biopolymers, particularly alginates (5). Alginate had been widely used as a food additive; beside this it has been used as a potential polymer for the development of controlled-release systems. Hydration of alginate with media leads to the formation of gelatinous mass which act as retardant material for the drug to diffuse out.

Many researches have been done where alginate proved to be promising agent in retarding the drug release. Matrix tablets of sodium alginate by direct compression have been prepared (6-8).

The presence of pores in ceramic foams offers the possibility to use these porous ceramics as carriers for local and controlled delivery of drugs. This application is useful in treatment of many skeletal diseases. The incorporation of antibiotics, chemotherapeutica, NSAIDs and growth factor in porous bone scaffolds is already been established (9-14). Ammonium carbonate (AC) had been already used as a pore forming to produce porous microparticles of bendroflumethazide by spray drying (15).

Metoprolol tartrate (MT) is a β-selective adrenergic blocking agent and is prescribed widely in cardiovascular diseases like hypertension, angina pectoris, arrhythmias and myocardial infractions. Conventional tablets of metoprolol tartarate has been reported to exhibit fluctuations in plasma drug levels resulting in side effects or reduction in drug concentrations at the receptor sites [16]. So maintenance of a constant plasma concentration of a metoprolol tartarate is important in ensuring the desired therapeutic response. Since half life of metoprolol tartarate is 3-4 h, multiple doses of the drug are needed to maintain a constant plasma concentration for a desired therapeutic response. It has been reported that metoprolol tartarate absorption in the duodenum and jejunum is directly proportional to dose availability (16-18).

In the present study, controlled release porous tablets of metoprolol tartrate (MT) were prepared by direct compression technique using a pore forming agent Ammonium carbonate

(AC) so as to maintain a constant plasma concentration within desired period to ensure desired therapeutic response and should provide a zero order drug release for twice daily administration of MT. Influence of pore forming agent on properties of tablets (disintegration, hardness and drug release) were investigated.

MATERIALS AND METHODS

Material

Metoprolol tartrate was obtained as a gift sample from Astra Zeneca Pvt Ltd. Banglore. Sodium alginate, ammonium carbonate and directly compressible microcrystalline cellulose (MCC), were procured from Loba Chemie Pvt Ltd. Mumbai. Other reagents were of analytical grade.

Methods

Preparation of porous tablets

Porous tablets were prepared by direct compression method. All the ingredients were passed through # 44-mesh separately. Then the ingredients were weighed and mixed in geometrical order and compressed into tablets of 250 mg using 8mm round flat punches on 10-station rotary tablet machine (Rimek Mini Press, Mumbai). Ammonium carbonate (AC) previously sieved was used as pore forming agent. Tablets are washed with water twice for 10 sec for aqueous extraction of AC from the tablets in order to create pores. Different formulations were prepared and shown in Table 1.

Table 1. Formulation chart of porous tablets prepared.

S.No	Formulation Code	Sodium Alginate (mg)	Ammonium Carbonate (mg)	Microcrytalline Celluose (mg)	Talc (mg)	Magnesium Stearate (mg)
1	A1	50	15	177	4	4
2	A2	100	15	127	4	4
3	A3	150	15	77	4	4
4	B1	50	45	147	4	4
5	B2	100	45	97	4	4
6	B3	150	45	47	4	4
7	C1	50	75	117	4	4
8	C2	100	75	67	4	4
9	C3	150	75	17	4	4

Drug loading of Metoprolol tartrate (MT) in porous tablets

Drug was loaded in the tablets by spiking method. Metoprolol tartrate was incorporated in the tablets as highly water soluble model drug. Therefore, 100 µl of an aqueous drug solution of metoprolol tartrate (3%, w/v) was spiked on one side of the tablet. After absorption of the liquid into the porous inner structure of the SA tablet, tablets were oven-dried for 6 h at 50°C. After drying of the porous tablets, the same procedure was done at the other side of the tablet to load the drug.

The surface tension of the drug solutions was previously determined by dynamic 'Wilhemy Plate' method (19).

Coating of porous tablets

Enteric coating of all tablets formulations loaded MT was done by spray coating in a conventional coating pan.

In brief coating solution was prepared by mixing Eudragit S100 with acetone for 1h using stirrer. After an hour, triethyl citrate (TEC), 2%, was added and stirring was continued for 30 min. The tablets were coated in a conventional pan with 20 RPM, at a coating solution spray rate of 2ml/ min and inlet temperature of 60°C; Coating of tablets was continued till the weight gained was 2% per average weight of the tablet. The coated tablets were dried in an oven at 35°C for one day and stored in air-tight container.

Evaluation of precompression parameters of powders blends and postcompression parameters of prepared porous tablets

Precompression parameters of powder blends and other physical parameters such as weight variation, hardness, friability, disintegration time, wetting time, and drug content were investigated.

Angle of repose

Static angle of repose was determined according to the fixed funnel and free standing cone method, where by accurately weighed powder bed (3 g) were carefully poured through the funnel with its tip at 2-cm height, H, until the apex of the conical heap so formed just reached the tip of the funnel (20).

The mean diameter, 2R, of the base for the powder cone was measured and the angle of repose (θ) was calculated using the equation,

$$\text{Tan } \theta = (H / R) \quad \text{(eq. 1)}.$$

Bulk Density

Both poured (or fluff) bulk (Do) and tapped bulk densities (D_T) were determined, according to the method reported, whereby a quantity (3 g) of powder bed from each formula, previously lightly shaken to break any agglomerates formed, was introduced into a 10-mL measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2-second intervals. The tapping was continued until no further change in the volume was noted.

Hausner's Factor

Hausner found that the ratio D_T / Do was related to interparticle friction and, as such, could be used to predict powder flow properties (21). In order to determine the uniformity in weight of tablets, 20 tablets of each formulation were randomly collected and weighed using class A weight balance and their percentage variation was determined. Hardness of tablets was also determined using Erweka Hardness Tester. Ten tablets of each formulation were used and the average hardness value was determined. The tablets of each formulation were also subjected to friability testing employing Pharma Test Friabilator. Ten tablets were rotated in friabiliator (Model EF2, Electrolab, Mumbai, India) for 4 min at a speed of 25 rpm. The tabletes were dedusted, and the loss in weight due to fracture and abrasion was recorded as percentage weight loss (percent friablity). Triplicate measurements were conducted for each formulation. The acceptable limit of weight loss was not more than 1.00%.

Wetting Time

Wetting time was measured according to procedure used by Bi Y. et al.[8] with some modifications. Wetting time of uncoated porous tablet was measured. A piece of tissue paper folded twice was placed in a small culture dish (i.d. = 6.5 cm) containing 6 ml of water. A tablet was placed on the paper, and the time for complete wetting was measured (22).

Disintegration Time

Disintegration test was done in accordance with Indian Pharmacoepia 1996 for gastroresistant tablets. Coated tablets were placed in tubes and disintegration time was noted in pH 1.2 for first 1 h, tablets were observed for any cracking or disruption of coating. Subsequently tablets media were changed to pH 7.4 and test was further carried out to measure disintegration time of tablets. The disintegration time for six tablets was measured, and the average time and standard deviation were calculated for each. Test were done in triplicate (n=3).

Drug Content

In the case of drug content uniformity test, tablets were pulverized and then transferred into a 250-ml volumetric flask. The volume was adjusted with pH 7.4 phosphate buffer and kept on rotary shaker for 24 h in order to completely extract the drug. The mixture was filtered, and the drug was assayed spectrophotometrically at 222 nm (Shimadzu UV-1108).

Fourier Transform Infrared Radiation Measurements (FT-IR)

FT-IR analysis was carried out for pure drug and formulation using KBr pellet method on FT-IR spectrophotometer type Shimadzu model 8033, USA in order to ascertain compatibility between drug and polymer used.

Differential scanning calorimetry (DSC)

All dynamic DSC studies were carried out on DuPont thermal analyzer with 2010 DSC module. The instrument was calibrated using high purity indium metal as standard. The dynamic scans were taken in nitrogen atmosphere at the heating rate of 10°C/min heating rate of 10°C/min.

Scanning electron microscopic (SEM)

SEM photographs were taken with a scanning electron microscope Model Joel- LV-5600, USA, at the required magnification at room temperature. The photographs were observed to visualize the porous structure of the tablets.

In-vitro drug release studies

In vitro drug-release studies were performed by using a USP dissolution rate apparatus (apparatus 1, 100 rpm, 37± 0.5°C) in pH 1.2 hydrochloric acid buffer (900 ml) for 2 h as the average gastric emptying time. Then, the dissolution medium was replaced with a pH 7.4 phosphate buffer (900 ml) for rest of the dissolution studies till complete drug release was obtained. The amount of MT released from the tablets at different time intervals was determined spectrophotometrically at 222 nm (Shimadzu UV-1208). All experiments were done in triplicate (23).

RESULT AND DISCUSSION

Precompression parameters of powder blends and postcompression parameters of prepared porous tablets

The values of precompression parameters of powder blends evaluated were within prescribed limits and indicated good free flowing property as shown in Table 2.

Table 2. Precompression parameters of powder blends.

S.No	Formulation Code	Bulk Density (g/mL)	Tapped Density (g/mL)	Angle of Repose ± SD, n=3	Carr's Index (%) ± SD, n=3	Hausner's Ratio ± SD, n=3
1	A1	0.43 ± 0.027	0.65 ± 0.02	23.13 ± 1.86	14.17 ± 1.73	1.29 ± 0.07
2	A2	0.47 ± 0.046	0.71 ± 0.04	22.16 ± 2.56	15.23 ± 1.25	1.25 ± 0.08
3	A3	0.56 ± 0.016	0.73 ± 0.16	22.29 ± 1.37	16.33 ± 1.32	1.29 ± 0.03
4	B1	0.49 ± 0.026	0.68 ± 0.23	26.18 ± 1.81	16.21 ± 1.59	1.18 ± 0.05
5	B2	0.53 ± 0.062	0.69 ± 0.11	23.31 ± 1.53	17.22 ± 1.65	1.17 ± 0.07
6	B3	0.59 ± 0.087	0.71 ± 0.19	24.21 ± 2.76	17.03 ± 1.47	1.29 ± 0.05
7	C1	0.43 ± 0.061	0.72 ± 0.22	21.20 ± 2.16	17.22 ± 1.35	1.21 ± 0.09
8	C2	0.48 ± 0.049	0.76 ± 0.17	26.17 ± 2.06	18.65 ± 1.18	1.29 ± 0.07
9	C3	0.54 ± 0.017	0.79 ± 0.26	27.23 ±1.17	18.23 ± 1.56	1.27 ± 0.07

Bulk density varies between 0.43 ± 0.027 to 0.59 ± 0.087 g/mL for all batches of formulations prepared. Angle of repose and Carr's index are within limits ensuring good flow properties of precompression powder blends indicating its acceptability for direct compression of tablets. Post compression parameter of porous tablets was evaluated and shown in Table 3. Hardness of all prepared tablets varies between 6.4 ± 0.02 to 3.9 ± 0.06 Kg/cm^2. Friability varies between 0.001 ± 0.034 to 0.069 ± 0.12 % (USP limit < 1 %).

Table 3. Post compression parameters of prepared porous tablets.

Formulation Code	Hardness (Kg/cm^2) ± SD	Friability (%) ± SD	Disintegration Time (min)** ± SD	Wetting Time (Sec) ± SD	Weight Variation (mg) ± SD	Drug Content (mg) ± SD
A1	6.4 ± 0.02	0.001 ± 0.034	83	77	249 ± 1.03	29.58 ± 0.17
A2	5.8 ± 0.04	0.024 ± 0.24	67	65	248 ± 1.11	28.15 ± 0.18
A3	4.9 ± 0.01	0.033 ± 0.36	38	35	251 ± 0.32	29.18 ± 0.23
B1	6.2 ± 0.02	0.026 ± 0.13	71	66	251 ± 1.57	29.89 ± 0.45
B2	5.4 ± 0.06	0.059 ± 0.21	57	52	249 ± 1.65	29.13 ± 0.27
B3	4.3 ± 0.08	0.051 ± 0.29	29	24	251 ± 1.17	28.19 ± 0.85
C1	5.8 ± 0.06	0.069 ± 0.12	33	29	252 ± 1.25	28.94 ± 0.89
C2	4.8 ± 0.04	0.066 ± 0.17	26	19	249 ± 1.78	29.19± 0.67
C3	3.9 ± 0.06	0.056 ± 0.17	23	16	250 ± 1.88	28.99± 0.17

** Disintegration Time (min) for tablets in pH 7.4.

Wetting time was closely related to the inner structure of the tablets. It is shown that porous tablets with least amount of pore forming agent and with least amount of polymer (A1, B1, C1) in their respective batches showed longer wetting time as compared to other formulations prepared. It may be due to the fact that the amount of polymer and pore forming agent used in respective batches makes a compact mass harder on direct compression. Because

of this, the wetting fluid will take much longer time in order to penetrate the tablets surface due to the less porous structure of tablets. Due to the less amount of pore forming agent present, less porous structure were formed in tablets which in turns lead to less porosity of tablets. The same phenomenon was shown in other tablets formulations. More the amount of pore forming agent less the time taken by the tablets to absorb the media. It is clearly indicated that the amount of pore forming agent is inversely proportional to wetting time of prepared porous tablets as shown in
Figure 1.

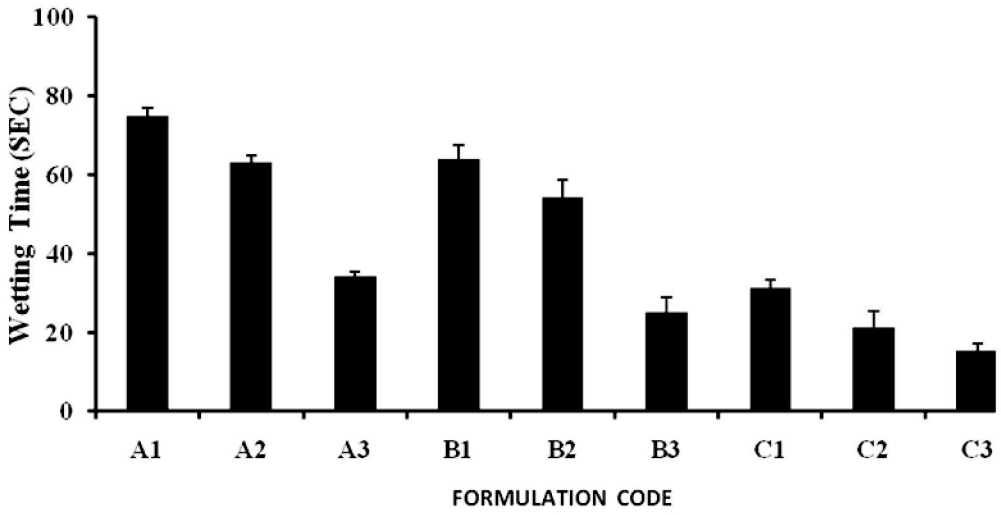

Figure 1. Wetting time of different porous tablet prepared.

MT solution was absorbed completely on all tablets surface. However in case of tablets having more amount of pore forming agents, solution was rapidly and completely absorbed. Interconnected pore network in the tablets structure made by presence of pore forming agent allowed the drug solution to penetrate and distribute fast and easily in tablets.

A trial has been done in order to see the effect of increased drug concentration on drug loading and time taken to load the drug. 8 % w/v solution of MT was prepared and was spiked on tablet surfaces. It was found that drug absorption on surface of tablets was complete but time taken to absorb the solution by tablets was slower as compared with 3 % w/v drug solution. The surface energy of all MT solutions (MT 3 % w/v, 58.13 ± 0.69 mN/m, MT 8 % w/v, 51.83 ± 0.84 mN/m) was lower compared to pure water (71.36 ± 0.17 mN/m), that mean that the highest drug concentration will have the lowest surface tension emphasizing that the drug molecules possess some tensio-active properties in solution form. Based on this study an improved liquid penetration should take place at higher drug concentrations. But on contrary another important aspect for drug penetration or uptake of solution is also determined by the phase tension between the solid phase (tablet surface) and the liquid phase (drug solution).

Due to the hydrophilic tablet surface (of polymer) there will be a competition between the tablet surface and the aqueous phase (water) to interact with the hydrophilic part of the drug molecules; an important factor which increases the phase tension between liquid phase and solid phase. Since this competition will increase at higher drug concentrations in solutions, an increase in phase tension accounts for the slower absorption of these drug solutions. These results were similar to findings by Barnes and Gentle (24).

FT-IR and DSC Studies

Compatibility between the drugs, polymers and other excipients used was studied by using FT-IR spectroscopy. The drug, MT exhibited general characteristic peaks. The characteristic peaks of pure drug were compared with the peaks obtained for their respective formulation. From the FT-IR peaks it can be concluded that the peaks of pure drug and formulations were found to be similar indicating that there was no significant interaction between drug and polymer used shown in Figure 2. MT has exhibited IR spectrum as a broad band around 3440.77 cm^{-1} for aliphatic C-H stretch, which is shown at 3438.37 cm^{-1} in the formulation , O-CH3, C-H stretch at 2934.24 cm^{-1} in pure drug , 2929.67 cm^{-1} in the formulation thus ruling out any interactions between drug and polymer used. FTIR studies completely show the drug stability during the direct compression technique.

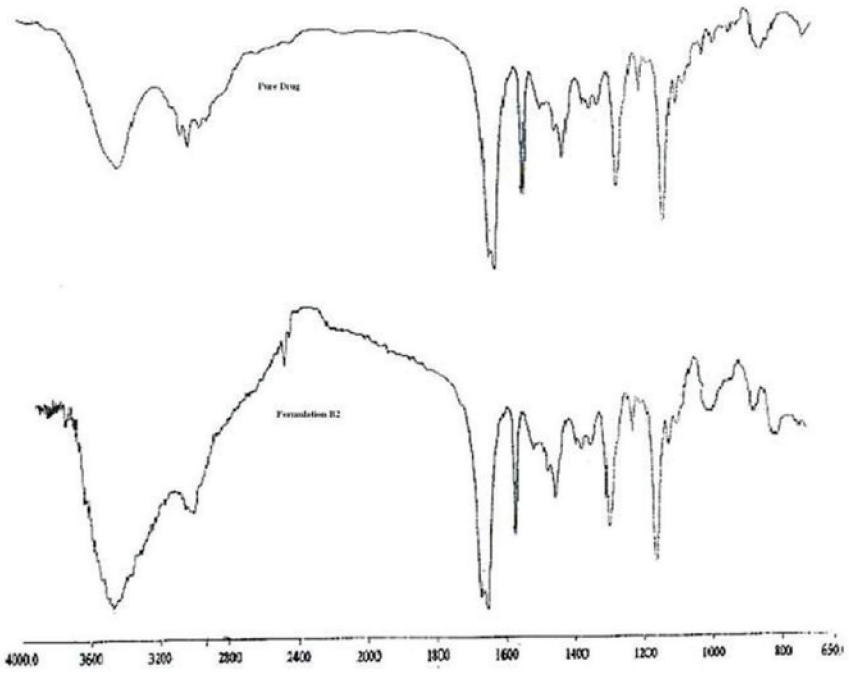

Figure 2. FT-IR studies of pure drug and formulation B2.

The DSC thermogram obtained by studies for the pure drug MT showed sharp endotherm at 122.9°C which correspond to its melting, and thermogram of the formulation showed the endotherm at 121.9°C as shown in Figure 3. As melting point of MT and that of the formulation are closer it reveals that there is no interaction between the drug and excipients used in study.

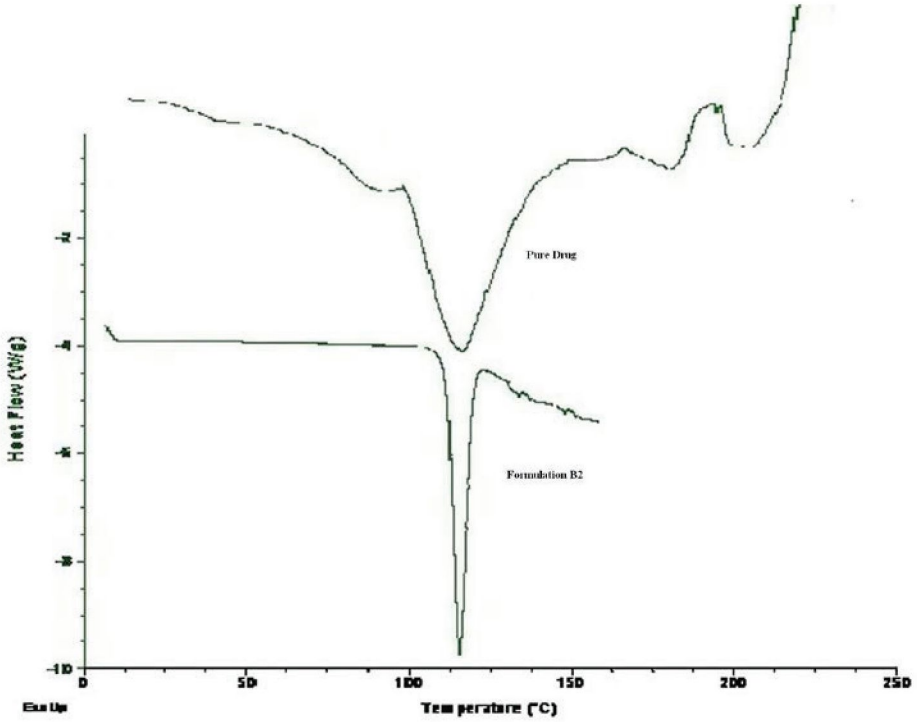

Figure 3. DSC thermograms of pure drug and formulation B2.

Scanning electron microscopic (SEM)

SEM analysis shows the porous surface of prepared SA porous tablets as shown in Figure 4. It is clearly shown from the SEM image that pores are successfully created in the tablets by dipping the tablets in aqueous solution (by aqueous extraction of pore forming agent) through which AC had been leached out and further drug can be loaded in the porous tablets. SEM had given a clear picture showing major and minor pore with different pore size.

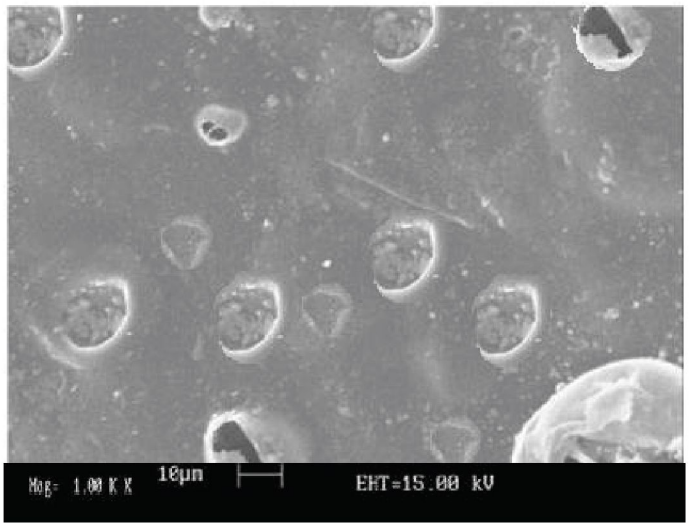

Figure 4. SEM showing the porous surface of SA tablets at magnification of 10µm.

Effect of the level of pore forming agent on hardness of porous tablets

Hardness of all prepared porous tablets varies between 6.4 ± 0.02 to 3.9 ± 0.06 Kg/cm^2. Effect of pore forming agent on various tablets hardness was shown in Figure 5.

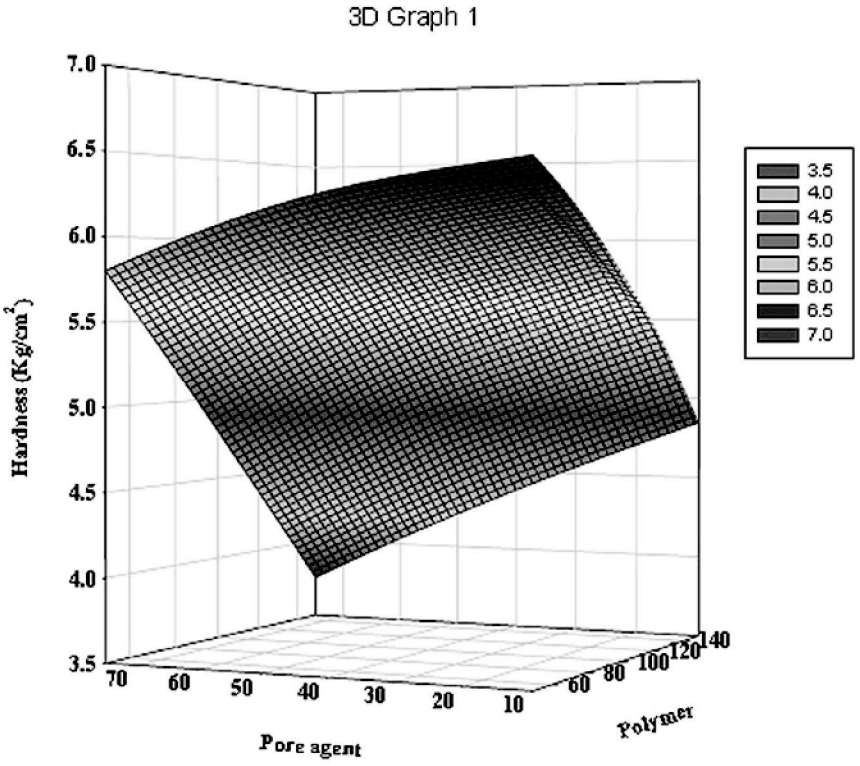

Figure 5. Response surface curve showing effect of the level of pore forming agent on hardness of porous tablets.

It is found that as we increase the amount of pore forming agent in tablets preparations, hardness goes on decreasing. Formulations A1 , B1 and C1 is composed of fixed amount of SA with varying concentrations (increasing) of AC (pore forming agent) as shown in Table 1. These formulations show maximum hardness but in decreasing order. A1 shows maximum hardness of 6.4 ± 0.02 Kg/cm^2, B1 showing 6.2 ± 0.02 Kg/cm^2 and C1 showing 5.8 ± 0.06 Kg/cm^2. All batches show same type of results. In case of formulation A2, B2 and C2 having same amount of SA but with varying concentrations (increasing) of AC (pore forming agent) the same results came into finding. A2 showing the maximum hardness of 5.8± 0.04 Kg/cm^2, B2 showing 5.4 ± 0.06 Kg/cm^2 and C2 showing 4.8 ± 0.04 Kg/cm^2. Hence it is clearly indicated that as we increase the amount of pore forming agent there will be more porous structure of tablets available thereby increasing the porosity of tablets thus there will be decrease in hardness of tablets.

Effect of the level of pore forming agent on disintegration time of porous tablets

Disintegration time (DT) is another parameter by which the porous structure of tablets can be defined. DT varies between 83 min to 23 min for prepared batches of tablets in pH 7.4. DT was first carried out in pH 1.2 to for 1 h to observe any cracking, deformity of tablets or any disruption of coating. It was found that there was no cracking or any other changes in physical appearance of tablets in pH 1.2.

The DT was in accordance with the results obtained in wetting time. Tablets that are having more wetting time took much longer time to disintegrate as compared to other tablet

formulations. More the amount of pore forming agent present in tablets less the time taken by the tablets to disintegrate. As we increase the amount of pore forming agent there will be more porous structure of tablets available thereby increasing the porosity of tablets, thus disintegration media will easily ingress into the tablets and helps the tablet to disintegrate in less time. Whereas in case of tablets having less amount of pore forming agent there will be not enough porosity of tablets structure in order for media to easily penetrate the tablet surface for disintegration.

Effect of pore forming agent on disintegration time of porous tablets was shown in Figure 6. As we increase the amount of pore forming agent in tablets preparations DT of porous tablets goes on decreasing.

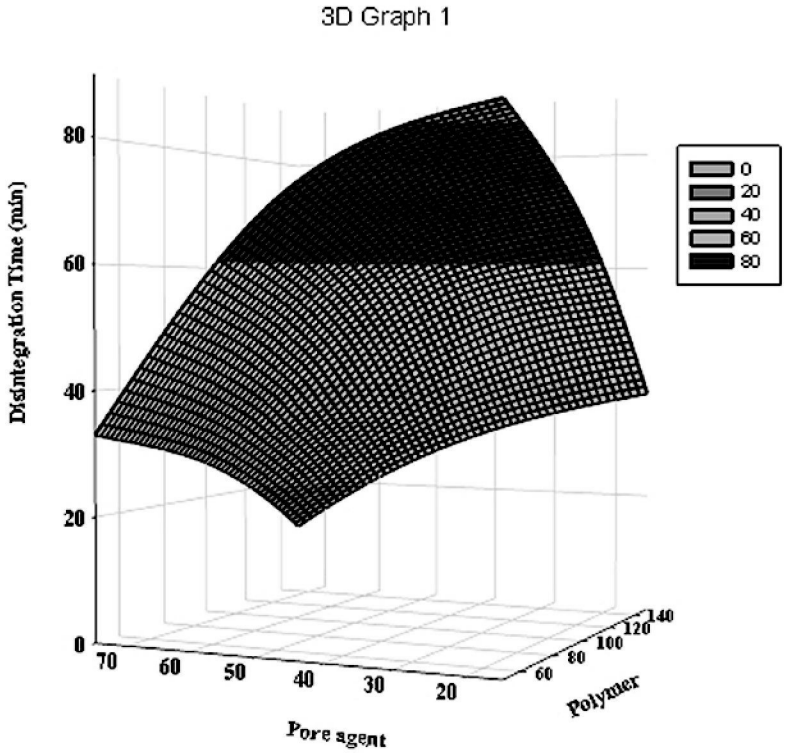

Figure 6. Response surface curve showing effect of the level of pore forming agent on disintegration time (DT) of porous tablets prepared.

Formulations A1 , B1 and C1 are composed of fixed amount of SA with varying concentrations (increasing) of AC (pore forming agent) as shown in Table 1. These formulations show maximum DT but in decreasing order. A1 shows maximum DT of 83 min, B1 showing 71 min and C1 showing 33 min. All batches show same type of results. In case of formulation A2, B2 and C2 having same amount of SA but with varying concentrations (increasing) of AC (pore forming agent) the same results came into finding. A2 is showing the maximum DT of 67 min, B2 showing 57 min and C2 showing 26 min. Hence it is clearly indicated that as we increase the amount of pore forming agent, there will be decrease in DT of porous tablets.

In Vitro drug release studies

Drug release of all prepared porous tablets was shown in Figure 7. It is clearly shown that from all batches of porous tablets prepared, no drug release took place in first 2 h at pH 1.2 because of the enteric coating of porous tablets by Eudragit S100. The enteric coating hindered the drug release in stomach. This shows that enteric coating by Eudragit S100 (2% w/v) done was sufficient enough and efficiently prevents the release of drug from porous tablets at gastric pH 1.2. Drug release started after changing dissolution media pH to 7.4. At pH 7.4 Eudragit

S100 enteric coat get dissolved as it is the characteristic of Eudragit S100 to get dissolved above pH 7. Dissolution of enteric coat brings the tablets surface in direct contact with the dissolution media.

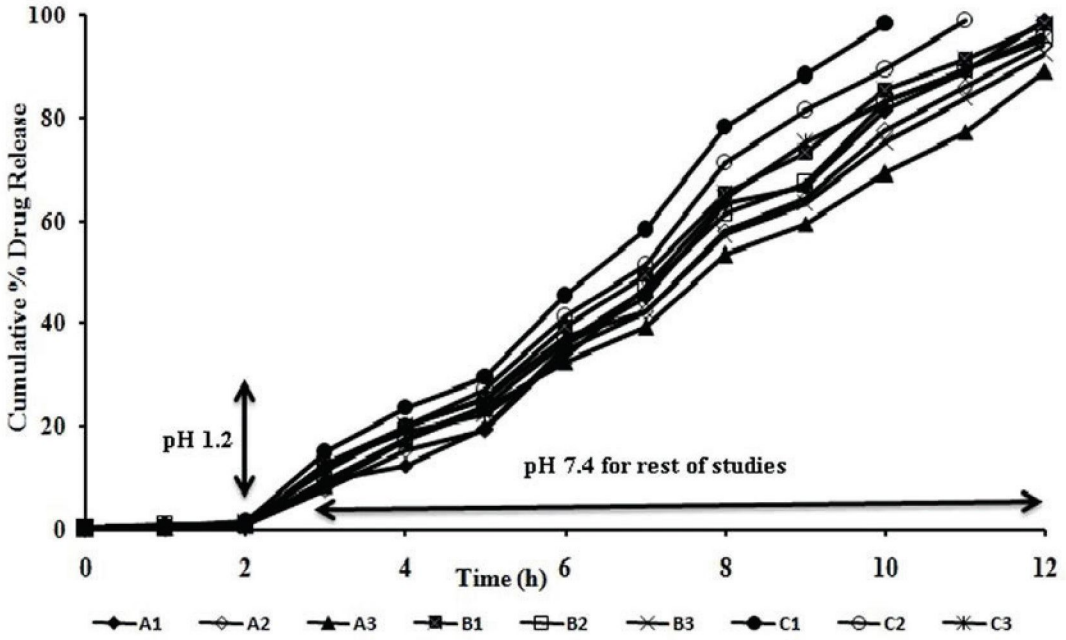

Figure 7. In vitro drug release profile of all batches of porous tablets.

It is clearly shown from Figure 7. that drug from the tablets were released in controlled manner which is due to the hydration ability of alginate, which on coming in contact with media which leads to the formation of gelatinous mass which act as retardant material for the drug to diffuse out.

Effect of the level of pore forming agent on in-vitro drug release of porous tablets prepared

Response curves clearly shown in Figure 8 clearly shows that formulation having least amount of polymer (50 mg) with maximum amount of pore forming agent (75 mg) will show drug release will be more and fast. As we goes on increasing the polymer concentration and reducing the pore agent concentration drug release will decrease. Same findings we can see in the drug release pattern are shown in Figure 7.

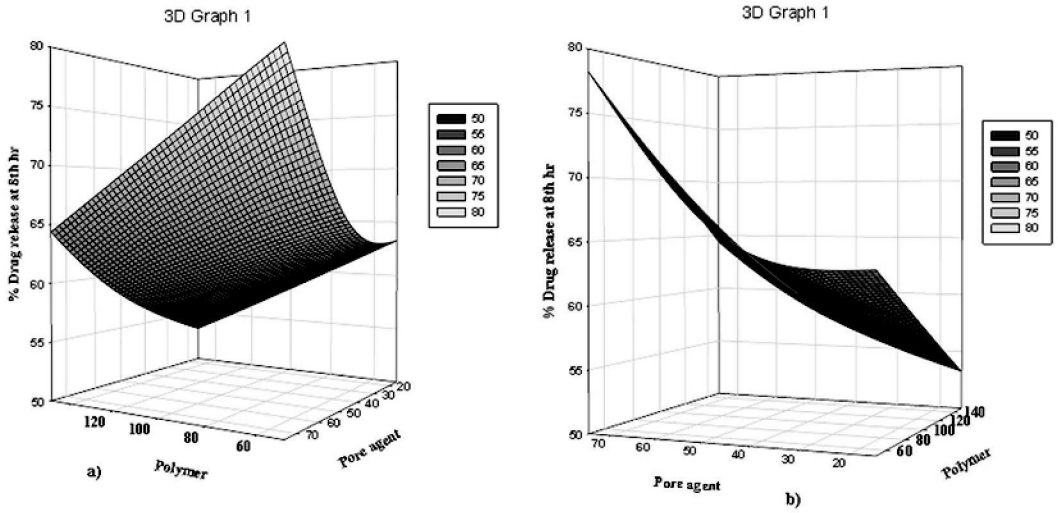

Figure 8. Response surface curve showing effect of the level of pore forming agent on dissolution of porous tablets prepared from different angles.

Drug release was found to be less in case of formulations having maximum amount of polymer (150 mg) with least amount of pore forming agent (15 mg). It is due to less amount of pore forming agent which creates less porosity in tablets and due to the hydration ability of alginate, in contact with media which leads to the formation of gelatinous mass which act as retardant material for the drug to diffuse out. It is clearly shown from the *in-vitro* drug release studies that amount of AC (pore forming agent) affects the drug release. In case of formulation A1, B1 and C1 which is composed of same amount of SA but varying amount of AC (in increasing amount), drug release at 8^{th} h was about 62.53%, 65.29% and 78.45% respectively. Thus on increasing the amount of pore forming agent, drug release will increase as there will be more porous surface available for the drug to diffuse out. However in case of C1 formulation porous tablets do not maintain its integrity till 12 h. Drug was release totally in 10^{th} h as there is less amount of SA present to maintain the integrity of tablet and retard the drug release for more time as shown in Figure 7. In case of formulation A2, B2 and C2 which is composed of same amount of SA but varying amount of AC (in increasing amount), drug release at 8^{th} h was about 58.13%, 61.69% and 71.35%, respectively. It is clearly shown that on increasing the amount of pore forming agent, drug release will increase as there will be more porous surface available for the drug to diffuse. Same results were obtained for Formulation A3, B3 and C3.
Release kinetics of the porous tablets prepared is shown in Table 4.

The best fit model representing the mechanism of drug release from the porous tablets prepared was of zero order. This is further confirmed by Korsmeyer-Peppas model, the value of n is greater than 1 showing case II drug release or anomalous drug release indicating that to more than one mechanism for the drug release are involved, that is diffusion and erosion. Results of drug release were in accordance with previous findings (24).

Table 4. Release kinetics of metoprolol tartarate from Sodium alginate porous tablets.

S.No	Formulation Code	Zero Order (r^2)	First Order (r^2)	Higuchi (r^2)	Korsmeyer Peppas (n)
1	A1	0.9616	0.6941	0.7991	2.361
2	A2	0.9664	0.8055	0.8165	2.618
3	A3	0.9738	0.8496	0.8232	2.391
4	B1	0.9761	0.7768	0.8336	2.488
5	B2	0.9720	0.8115	0.8391	2.290
6	B3	0.9786	0.8320	0.7281	2.371
7	C1	0.9608	0.7898	0.7125	2.347
8	C2	0.9664	0.8054	0.6675	2.553
9	C3	0.9673	0.8195	0.8484	2.344

CONCLUSION

Porous tablets of metoprolol tartarate were obtained by direct compression of sodium alginate, using ammonium carbonate as pore forming agent. This can be used as a carrier for low dosed tablets for twice daily administration of metoprolol tartarate. Drug was successfully incorporated in the tablets by spiking the drug solution on surface of tablets. Pre compression parameters for the powders blends to make the porous tablets were evaluated and were found to be within prescribed limits, indicating good free flowing property. Hardness of all prepared tablets varies between 6.4 ± 0.02 to 3.9 ± 0.06 Kg/cm^2. Friability varies between 0.001 ± 0.034 to 0.069 ± 0.12 % (USP limit < 1 %). Considerable effect of pore forming agent on hardness, disintegration time and drug release of porous tablets was found. It has been found that a increase in concentration of pore forming agent leads to decrease in hardness and disintegration time and will increase the drug release at a particular time level. SEM confirmed the formation of open pores with different pore size which makes the media to easily go inside the porous structure of tablets, making the porous tablets as a good candidate for low dosed drugs. Drug release from the porous tablets prepared follows zero order mechanism. Korsmeyer-Peppas model showed case II drug release or anomalous drug release indicating that two mechanism for the drug release are involved, that is diffusion and erosion. Thus porous carriers can be used for low dosed drugs by direct compression.

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