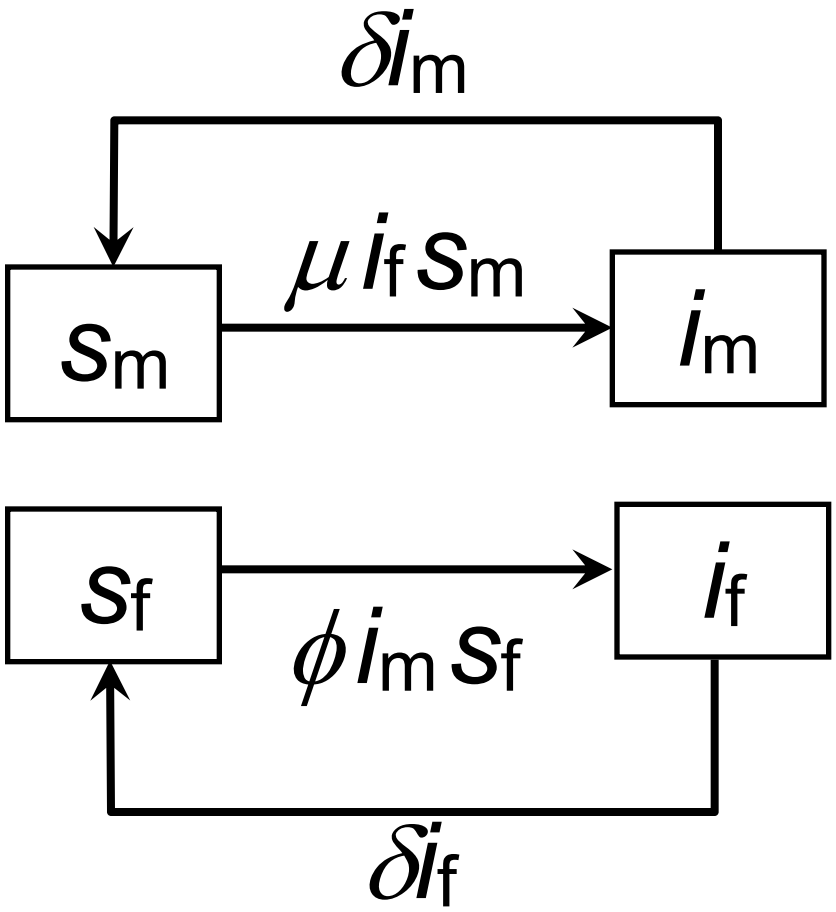
Male circumcision [MC]

- Auvert's MC trial at Orange Farm [Gauteng] indicated that MC reduces sexual transmission of HIV from female to male by 60%.
- SACEMA associates Williams, Lloyd-Smith and others modelled this situation and estimated the effects [on HIV infections, prevalence and deaths] of promoting MC as a public health policy.



S = susceptible
I = infected

The simplest model for men and women

No MC $\phi/\mu = 2$ 100% MC $\phi/\mu = 5$

If MC reduces transmission in one direction by a factor of π this is equivalent to a reduction in both directions by a factor of $1-\sqrt{(1-\pi)}$

MC is equivalent to a vaccine which reduces transmission by 37%

Superspreading and the effect of individual variation on disease emergence

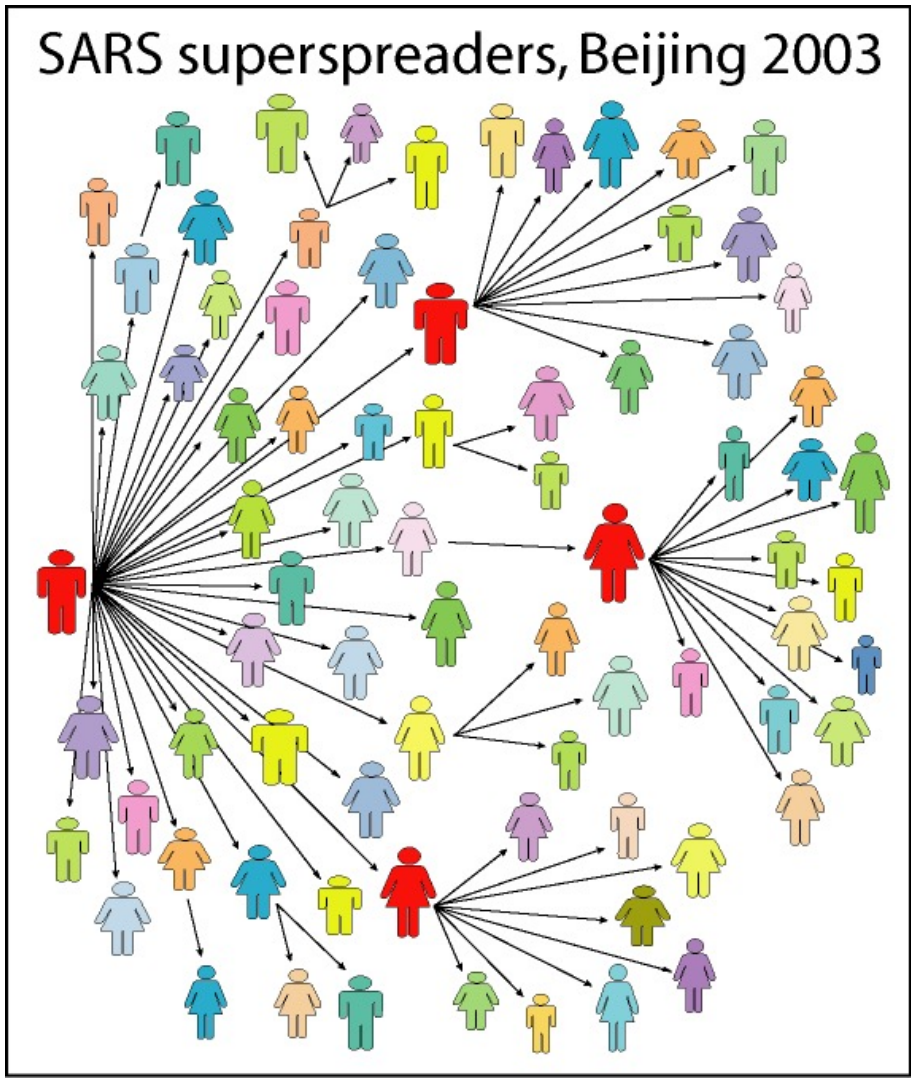
- Quantitative study of epidemic dynamics centres on the basic reproductive number, R_0
- Yet real epidemics (e.g. SARS in 2003) feature "superspreading" individuals who infect far more people than the average case.

How to incorporate superspreading in outbreak models?

How prevalent is superspreading for different diseases?

How does individual variation affect outbreak dynamics?

Superspreading and the effect of individual variation on disease emergence

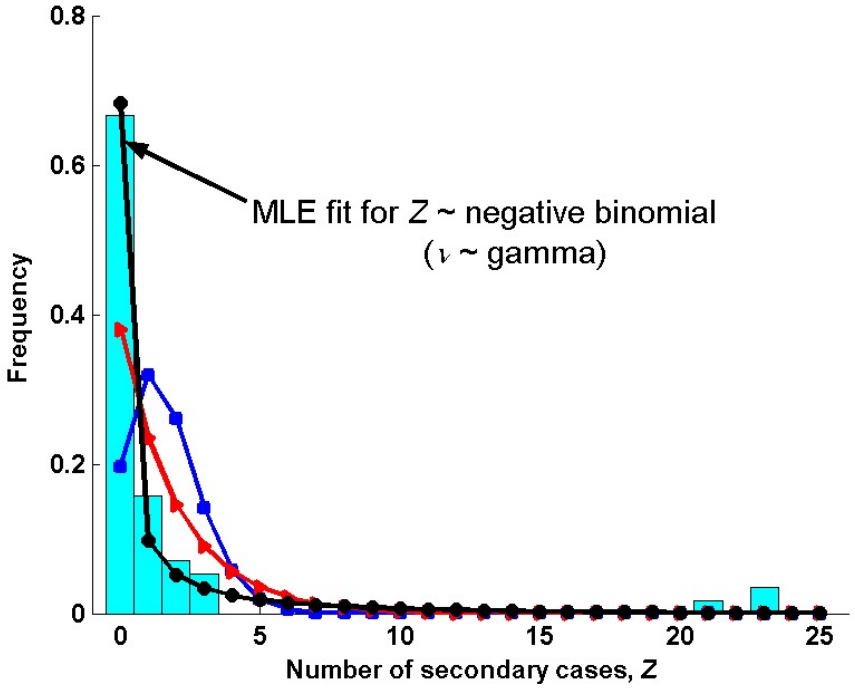


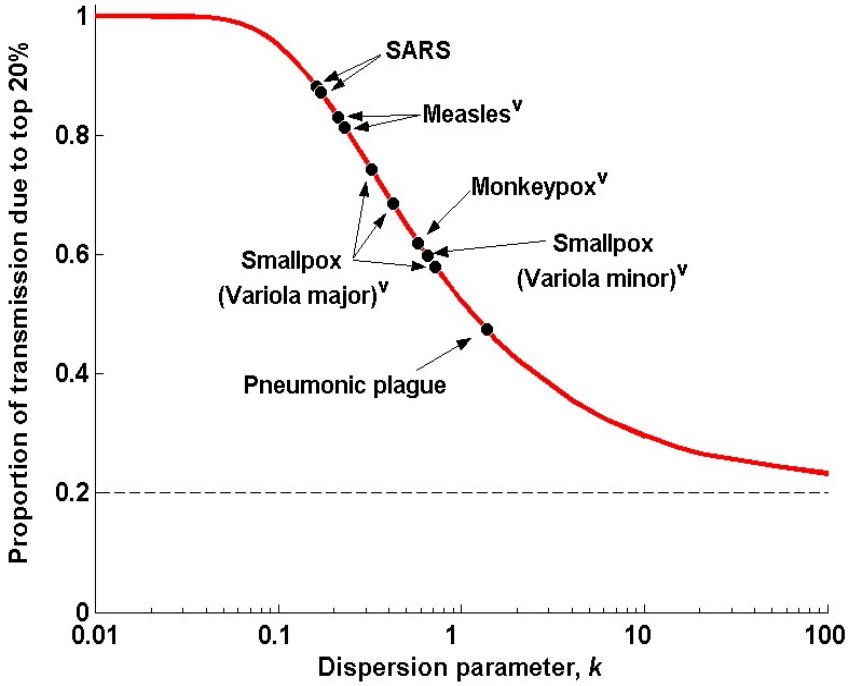
- "Normal" SARS cases infected 0 to 3 others, but "superspreaders" infected 10, 20 or more.
- Is superspreading an exceptional property of SARS, or common to all infectious diseases?
- How can this individual-level variation be modelled, and how does it affect outbreak dynamics?

Lloyd-Smith, Schreiber, Kopp & Getz *Nature* 438: 355-359.

Quantifying individual variation in transmission

1. Collect detailed transmission data for many diseases.
2. Apply maximum-likelihood estimation and Akaike's Information Criterion to select best statistical model for transmission data.
3. Compare diseases using model estimates.





Higher order implicit techniques

- All R-K techniques are explicit and hence run into trouble with stiff problems. What are the higher order implicit techniques?
- The simplest is the trapezoidal rule!
- The Euler method uses the slope of y(t) at t_k, the BE method uses the slope at t_{k+1}. If we average the two we can generate a second order rule!

Higher order implicit rules

- Thus: $y^{TR}_{k+1} = (y^{EM}_{k+1} + y^{BE}_{k+1})½$

  $y_{k+1} = y_k + ½h(f(t_k,y_k) + f(t_{k+1},y_{k+1}))$

  which is <u>implicit</u>.
- The error is a bit difficult to calculate, but eventually you get:

$$y^{TR}_{k+1} - y(t_{k+1}) = (1+ ½hJ)/(1 - ½hJ)*(y_k - y(t_k)) + O(h^3)$$

Higher order implicit rules

- Like the BE method, TR is stable for all J<0, but the amplification factor will approach –1 as hJ → – inf

$$amp^{BE} \sim 1/|Jh| \text{ as } Jh \rightarrow -\infty$$

$$amp^{TR} \sim \tfrac{1}{2}\, hJ/(-\tfrac{1}{2}\, hJ) = -1$$

which is close to instability! Thus the trapezoidal rule may be no better than the BE method for sufficiently stiff problems!

Higher order implicit methods

- What about higher order implicit techniques? If we just extended the TR to higher order, we would lose the infinite stability interval. Instead we use a different approach: Multi-Value methods.
- Consider the Taylor Series expansion:

$$y(t_{n+1}) = y(t_n) + h\, y'(t_n) + h^2/2\, y''(t_n) + h^3/6\, y'''(t_n) + h^4/24\, y^{iv}$$

Multi-Value methods

- The multivalue approach involves tracking each of these terms (the function and its derivatives) at every step. We can define the vector:

$$\tilde{y}(t_n) = \begin{pmatrix} y(t_n) \\ hy'(t_n) \\ \tfrac{1}{2} h^2 y''(t_n) \\ 1/6\, h^3 y'''(t_n) \end{pmatrix}$$

- This leads to the “Adams-Moulton” and “Gear” methods.

Adaptive Step Size Control

- We want to pick a step size which will achieve some desired accuracy. Unfortunately the required step size may change from point to point as the integration proceeds. This leads to the need for adaptive schemes for controlling the step size.
- To change the step size we need an estimate of the local integration error.

Adaptive Step Size Control

- Consider the 2-stage Runge-Kutta rule:

$$K_1 = h\, f(t_n, y_n)$$

$$K_2 = h\, f(t_n + h, y_n + K_1)$$

$$y_{n+1} = y + \tfrac{1}{2}(K_1 + K_2)$$

- The local error of this rule is $O(h^3)$ (overall, the rule is second order)
- Suppose we make one more evaluation:

$$K_3 = h\, f(t_n + h/2,\ y_n + (K_1 + K_2)/4)$$

- This is an estimate of the derivative at the midpoint of the interval!

Adaptive Step Size Control

- We can combine this with the other two evaluations to get a third order rule:

$$y_{n+1} = y_n + 1/6\,(K_1 + 4K_3 + K_2)$$

- Note the similarity of this rule to Simpson's rule!
- The local error is less than the difference between these two estimates:

$$\text{error} \sim \tfrac{1}{2}\,(K_1 + K_2) - 1/6\,(K_1 + 4K_3 + K_2)$$

$$= 1/3\,(K_1 - 2K_3 + K_2)$$

Adaptive Step Size Control

- If the error is greater than some chosen threshold, we reduce the step size. If the error is less than the tolerance, we may increase the step size.
- How do we determine the optimum step size? The local error in the 2-stage rule (which dominates the error estimate) is locally $O(h^3)$.
- If the error estimate is Δ and the allowed error is τ, then…

Adaptive Step Size Control

$$(h_{opt}/h)^3 \sim (\tau/\Delta)$$

- Thus, $h_{opt} \sim h(\tau/\Delta)^{1/3}$
- In practice, we pick our new h to be a little smaller than this value, say:

$$h_{opt} = 0.9h(\tau/\Delta)^{1/3}$$

- We must also set an upper and lower limit to h. The upper limit will just be some fraction of the total interval of integration.

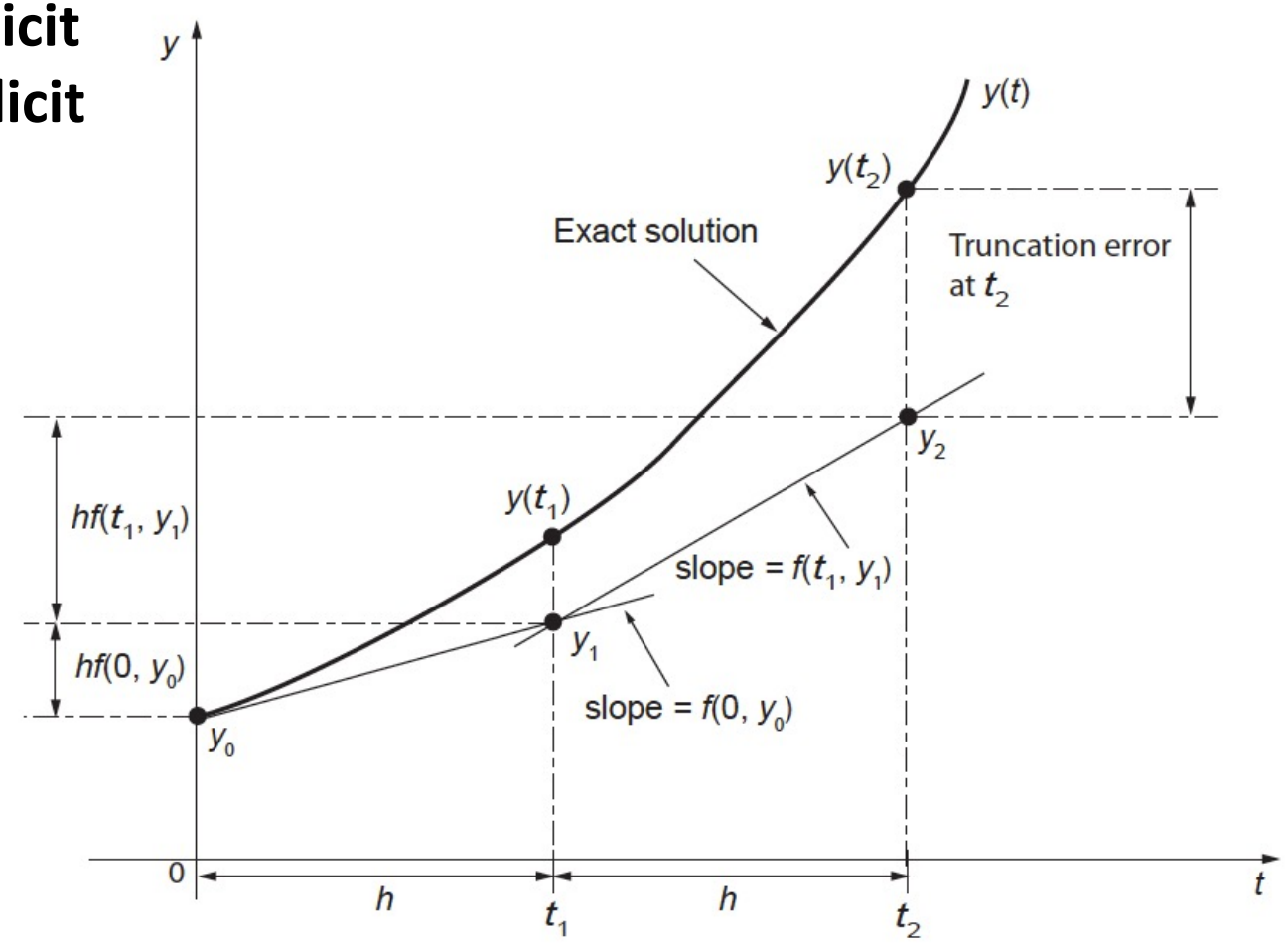
Adaptive Step Size Control

- The lower limit serves as a flag that we are approaching a singularity!
- This method is implemented in the Matlab routine “ode23.m”

Q1: Was this ODE integrated with an <u>explicit</u> or <u>implicit</u> Euler scheme?

A. Explicit

B. Implicit



Q2: Is this ODE stable or unstable?

A. Stable

B. Unstable

$$\frac{dy}{dt} = t - y, \qquad y(0) = 1.$$

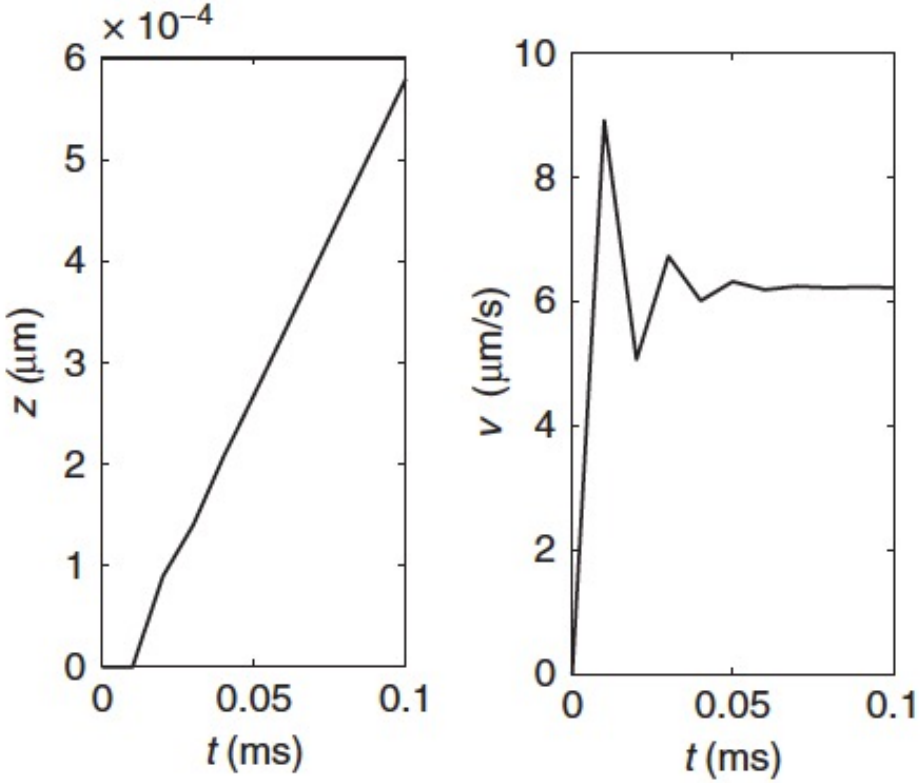
Q3: There is clearly some numerical error in the integrated solution for v(t). To remedy this, one could…

A. Increase the time step, h

B. Decrease the time step, h

C. Take the absolute value of v(t) at each time step

D. Rescale the units into cm/s.

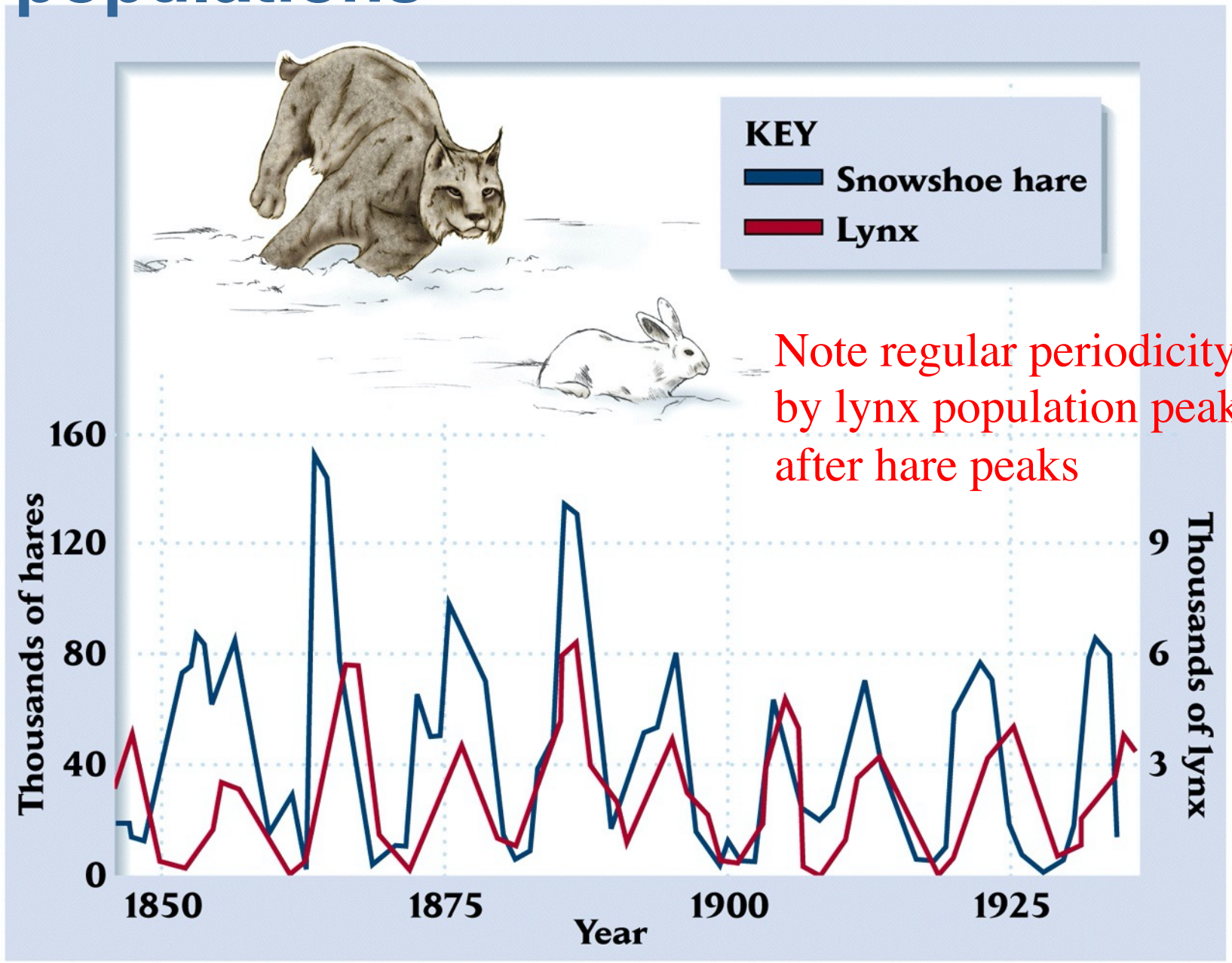


One of the most famous examples of predator-prey interactions illustrated by Canada lynx and snowshoe hare, in Canadian taiga (forest) biome

The Hudson's Bay Company provided the best long-term data set, showing the fluctuations of lynx and hare populations across Canada

(b)

Dramatic fluctuations of hare and lynx populations



Hare-lynx example

- Charles Elton's paper (1924), "Periodic fluctuations In the numbers of animals: their causes and effects", *British Journal of Experimental Biology*, was first (of MANY) publications to analyze this data set
- Are these cycles regular, i.e., with constant periodicity?
- What causes these cycles?
  - Interaction of predator and prey?
  - Hare-resource interaction? (hares feed on fir tree needles, and other vegetation)
  - Sunspot cycles?
  - Humans (as hunters) interacting with both predator and prey?

Lotka-Volterra Model cont.

- The Lotka-Volterra equations are a pair of first order, non-linear, differential equations that describe the dynamics of biological systems in which two species interact.
- Earliest predator-prey model based on sound mathematical principles
- Forms the basis of many models used today in the analysis of population dynamics
- Original form has problems

Predator-prey population dynamics are connected

Predators kill prey → *affects prey death rate*

$$dN_{prey}/dt = rN_{prey} - pN_{prey}N_{predator}$$

change in prey population

per capita rate of growth *without predation*

deaths due to predation

Predator-prey population dynamics are connected

Predators kill prey → *affects prey death rate*

$$dN_{prey}/dt = rN_{prey} - pN_{predator}N_{prey}$$

predation rate

- prey population size depends on number of predators
- with few predators, prey population grows
- with many predators, prey population shrinks

Predator-prey population dynamics are connected

Predators eat prey → *affects predator birth rate*

$$dN_{predator}/dt = cpN_{prey}N_{predator} - dN_{predator}$$

change in predator population

births due to predation

death rate

Predator-prey population dynamics are connected

Predators eat prey → *affects predator birth rate*

$$dN_{predator}/dt = cpN_{prey}N_{predator} - dN_{predator}$$

conversion rate *of prey to baby predators*

predation rate

- predator population size depends on number of prey
- with many prey, predator population grows
- with few prey, predator population shrinks

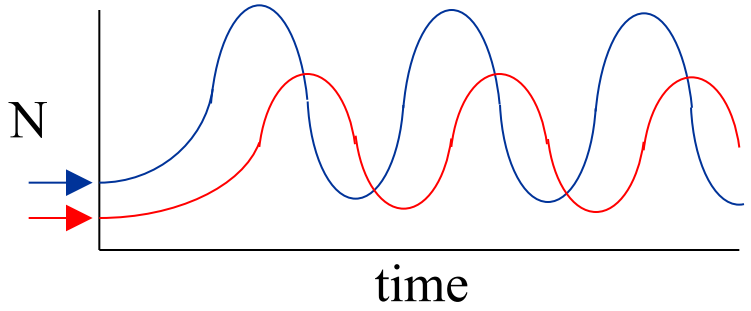
Predator-prey population dynamics are connected

Predators kill and eat prey → *affects prey death rate*
→ *affects predator birth rate*

$$dN_{prey}/dt = rN_{prey} - pN_{predator}N_{prey}$$

$$dN_{predator}/dt = cpN_{prey}N_{predator} - dN_{predator}$$

- with few predators, prey population grows
- with many prey, predator population grows
- with many predators, prey population shrinks
- with few prey, predator population shrinks



Q4: One of the following numerical integration schemes is unconditionally stable. Which one?

A. Euler implicit
B. Euler explicit
C. 4-stage Runga-Kutta

Q5: The integration scheme depicted below is known by all of the following names, EXCEPT ONE. Which one?

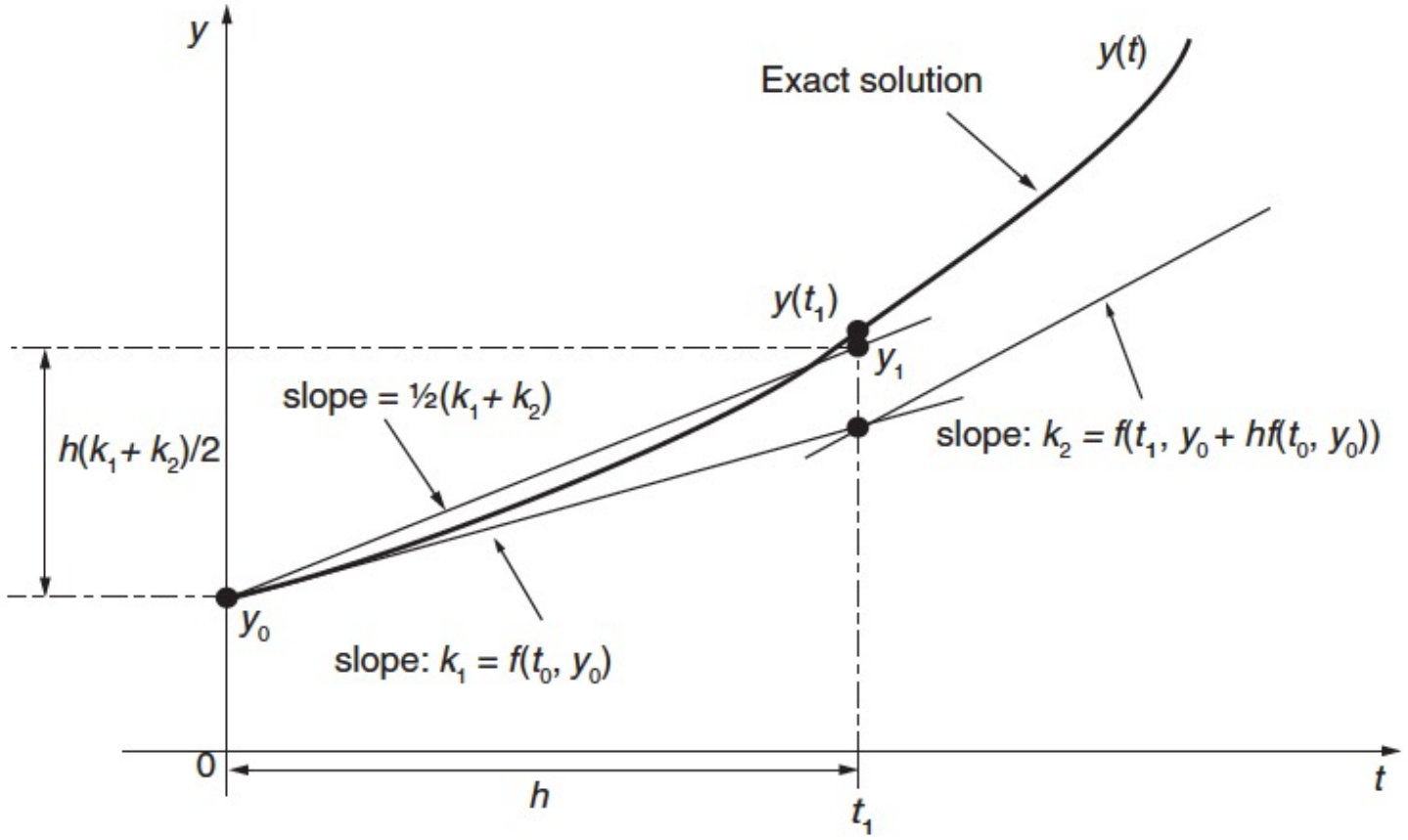
A. RK-2

B. Explicit modified Euler method

C. The trapezoidal rule

D. Heun's method

E. Adaptive step size method



Q6: Which integration scheme is implemented in the Matlab code below?

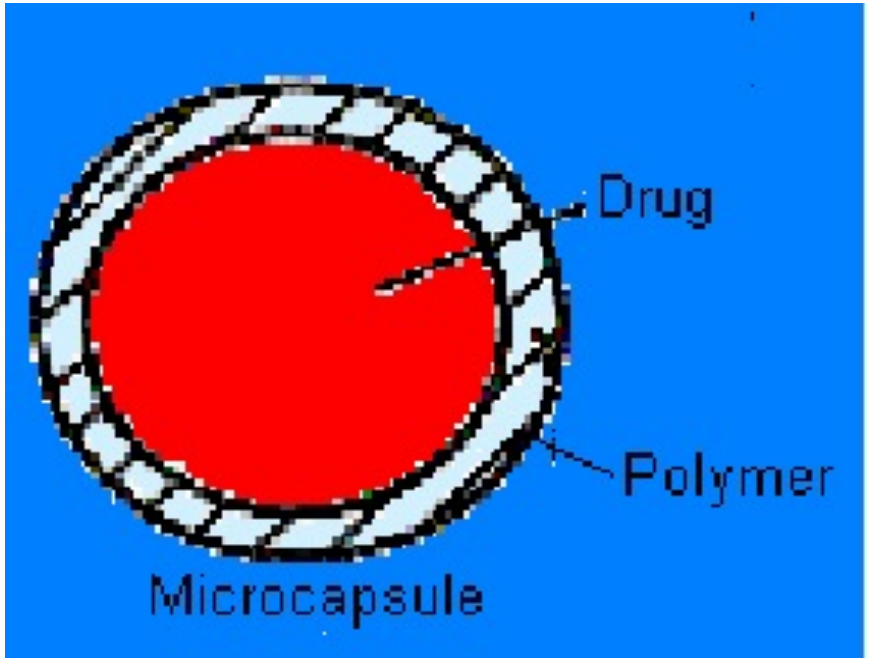
A. Euler implicit
B. Euler explicit
C. 4-stage Runga-Kutta
D. Heun's method

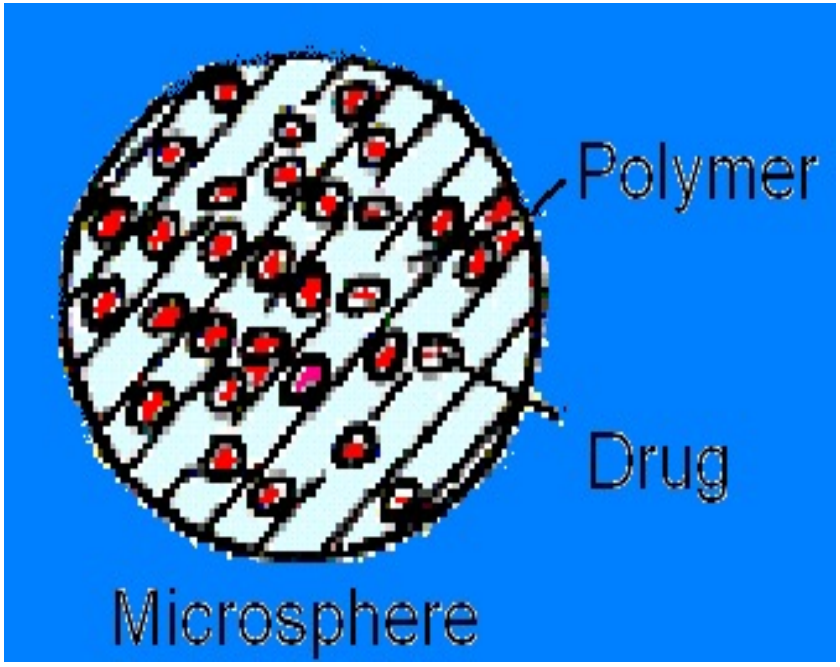
```
for k = 1:length(t)-1
    k1 = feval(odefunc, t(k), y(:,k));
    k2 = feval(odefunc, t(k) + h/2, y(:,k) + h/2*k1);
    k3 = feval(odefunc, t(k) + h/2, y(:,k) + h/2*k2);
    k4 = feval(odefunc, t(k) + h, y(:,k) + h*k3);
    y(:,k+1) = y(:,k) + h/6*(k1 + 2* k2 + 2* k3 + k4);
end
```

What Are Microspheres & Microcapsules

A Microcapsule has a drug located centrally within the particle, where it is encased within a unique polymeric membrane

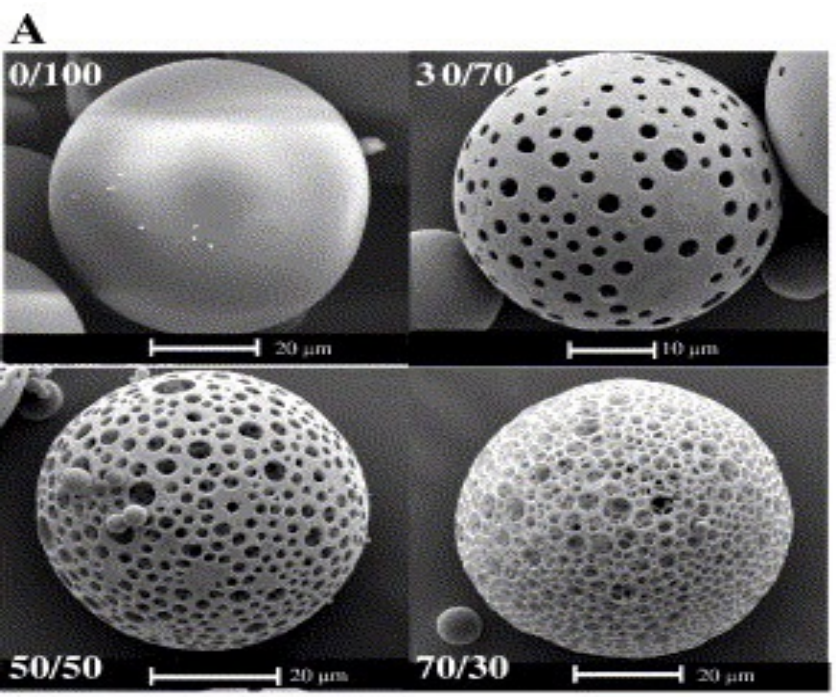
A Microsphere has its drug dispersed throughout the particle i.e. the internal structure is a matrix of drug and polymeric excipients

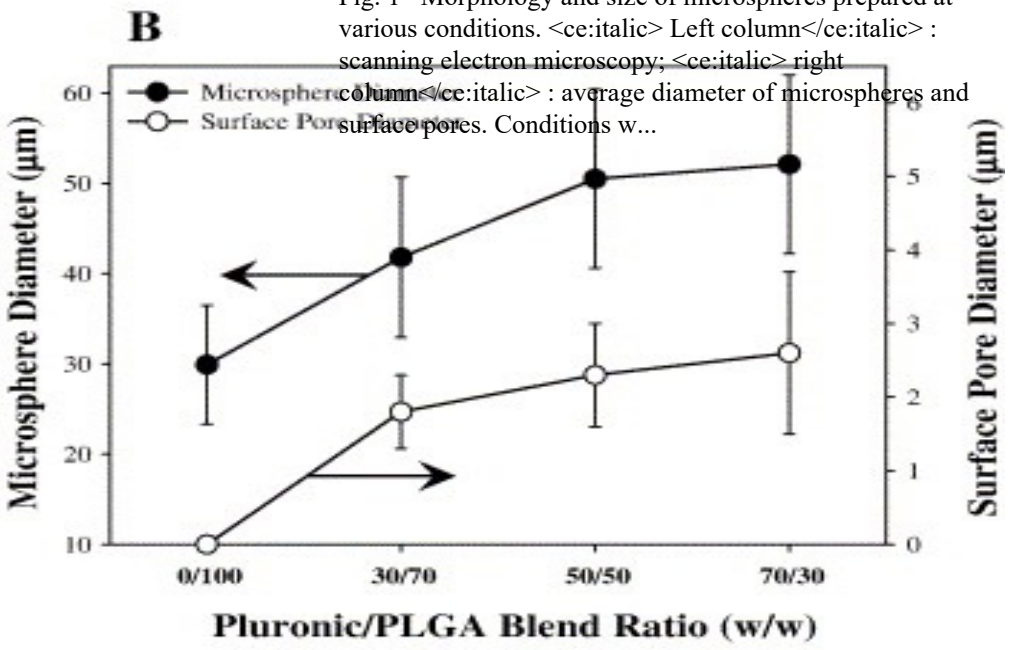


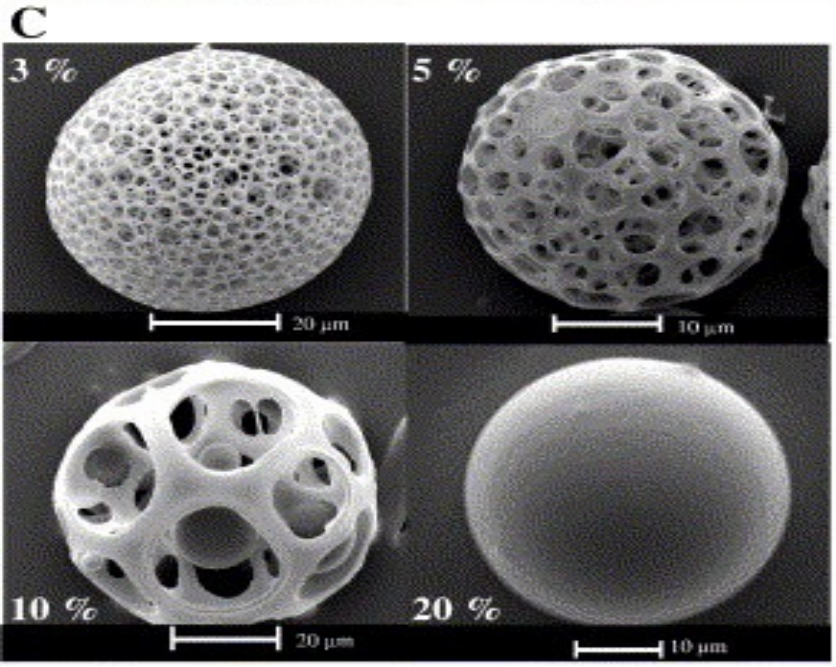


Rationale for Drug Encapsulation into Microparticles

- Production of novel product
- Protection of the product from the surrounding environment, hence improving the shelf life of the product and stability of the system
- Protection of environment from product, where active core material is hazardous or toxic
- Separation of components, allowing control of incompatibility of components
- Control rate of release of core material, by rupture of polymer wall e.g. by impact or long acting sustained release e.g. solution or diffusion
- Masking undesired properties of active component e.g. odour, taste
- Formation of solid systems e.g. conversion of liquid components to free flowing powders
- Targeting of site of release of active material







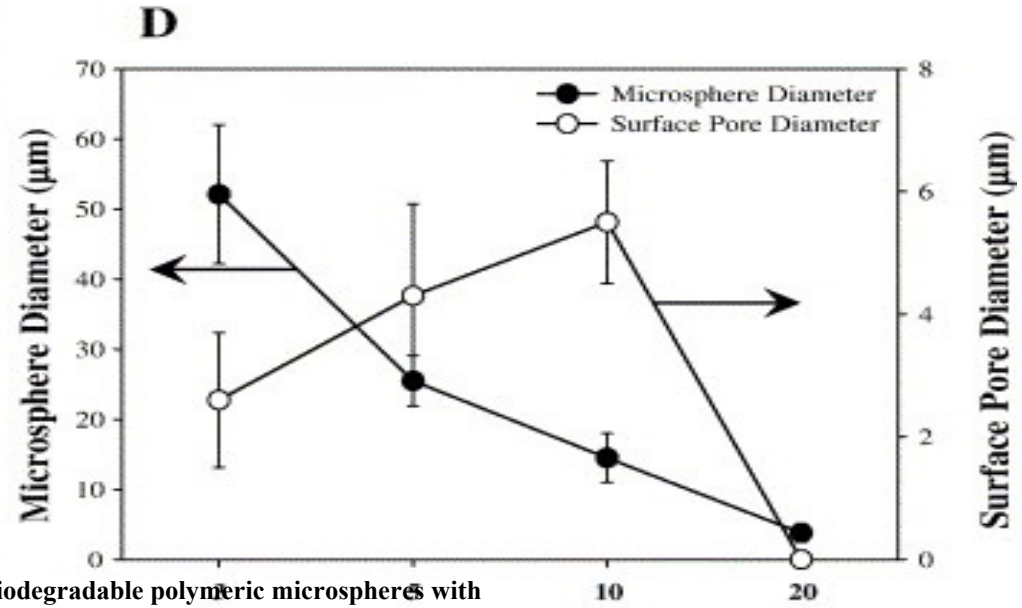


Fig. 1 Morphology and size of microspheres prepared at various conditions. <ce:italic> Left column</ce:italic> : scanning electron microscopy; <ce:italic> right column</ce:italic> : average diameter of microspheres and surface pores. Conditions w...

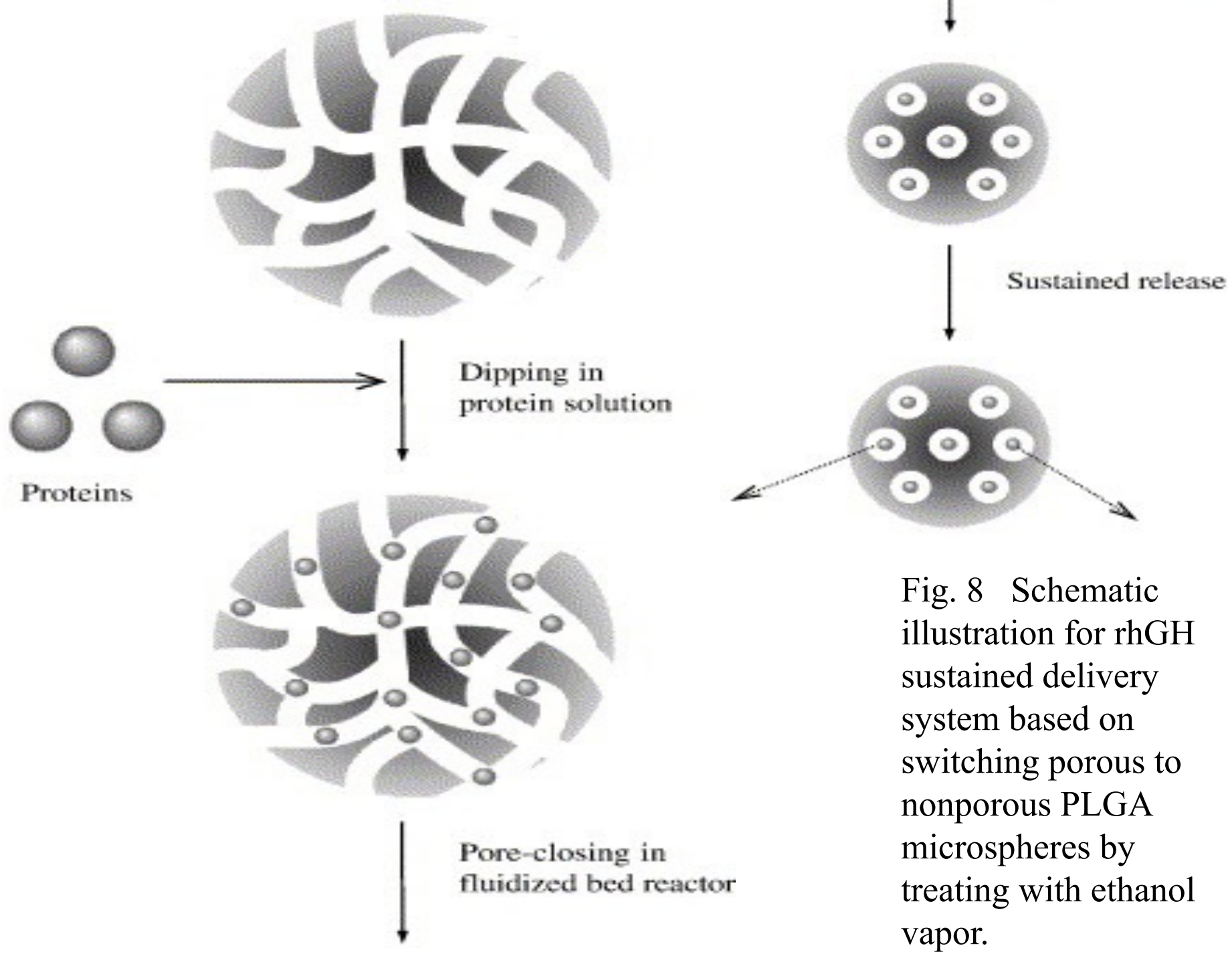
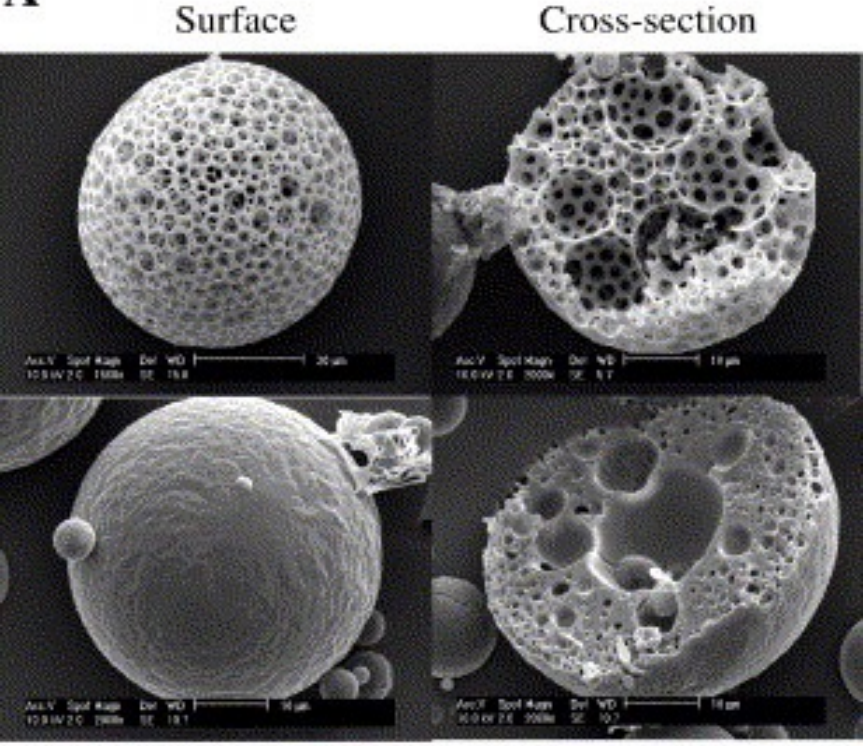


Fig. 8 Schematic illustration for rhGH sustained delivery system based on switching porous to nonporous PLGA microspheres by treating with ethanol vapor.



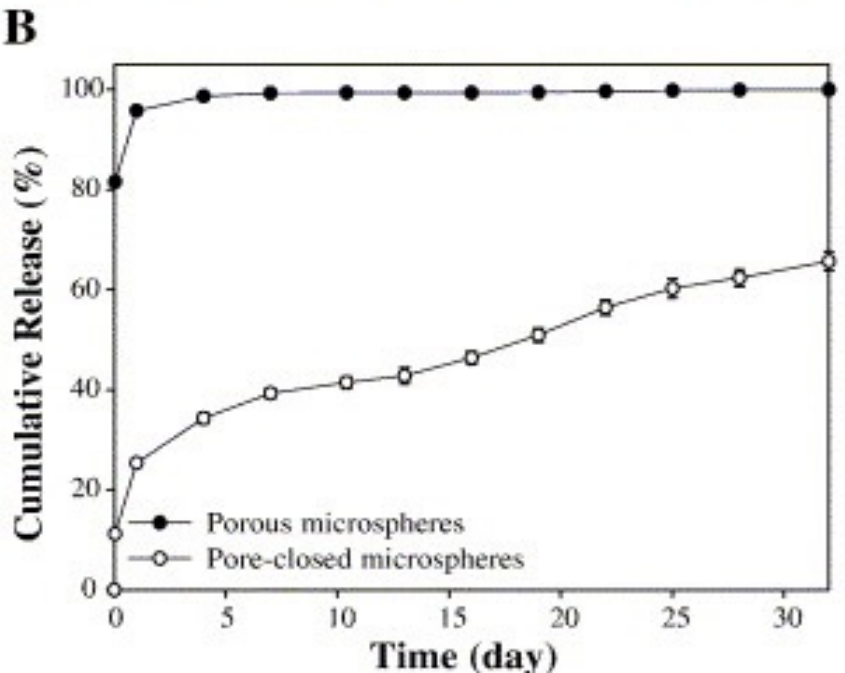


Fig. 2 (A) SEM images of the surface (left column) and cross-section (right column) of a porous microsphere (top) and pore-closed microsphere (bottom). (B) In vitro release profiles of rhGH from porous microspheres and pore-closed microspheres pr...

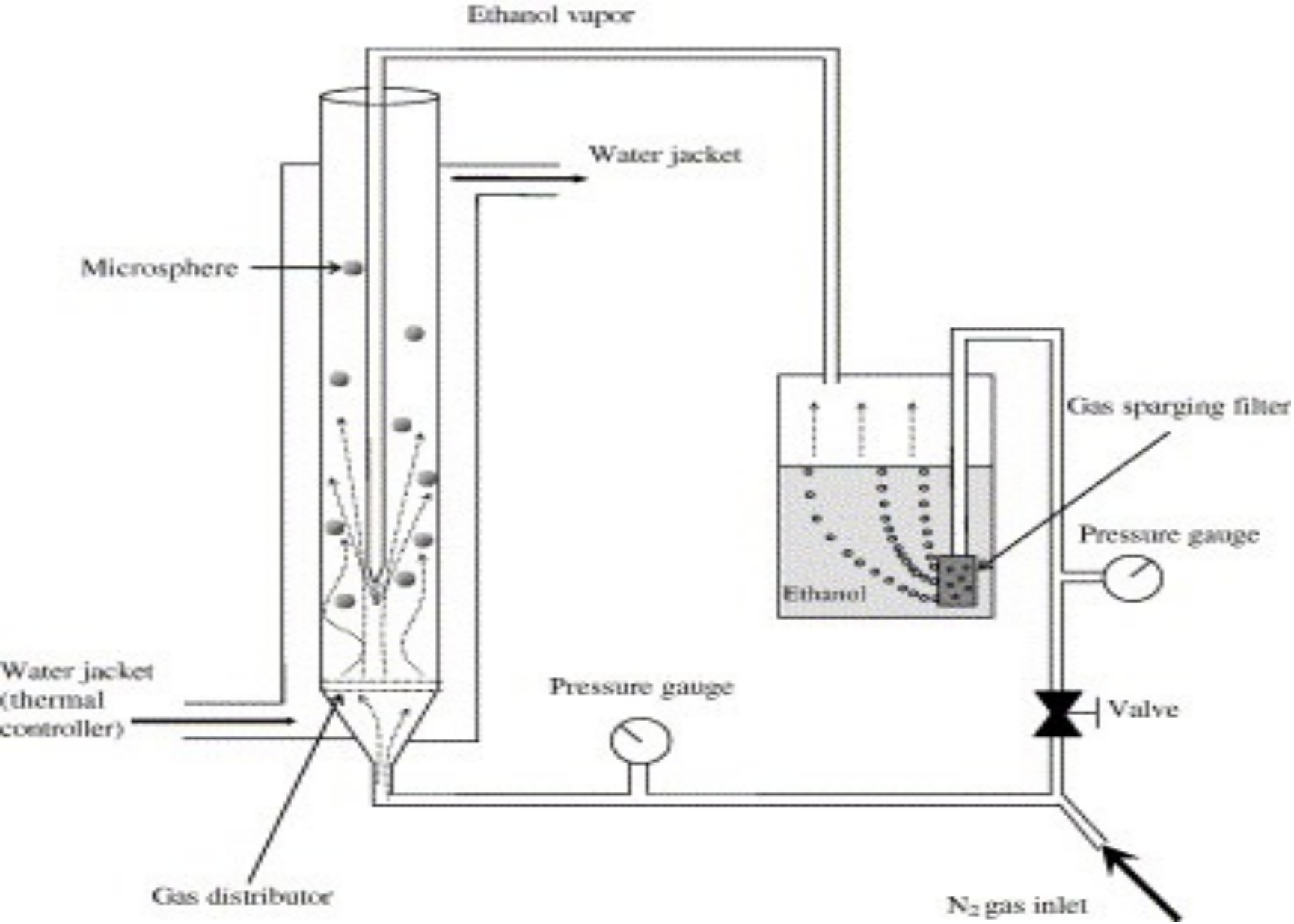


Fig. 3 A schematic diagram of the fluidized bed reactor.

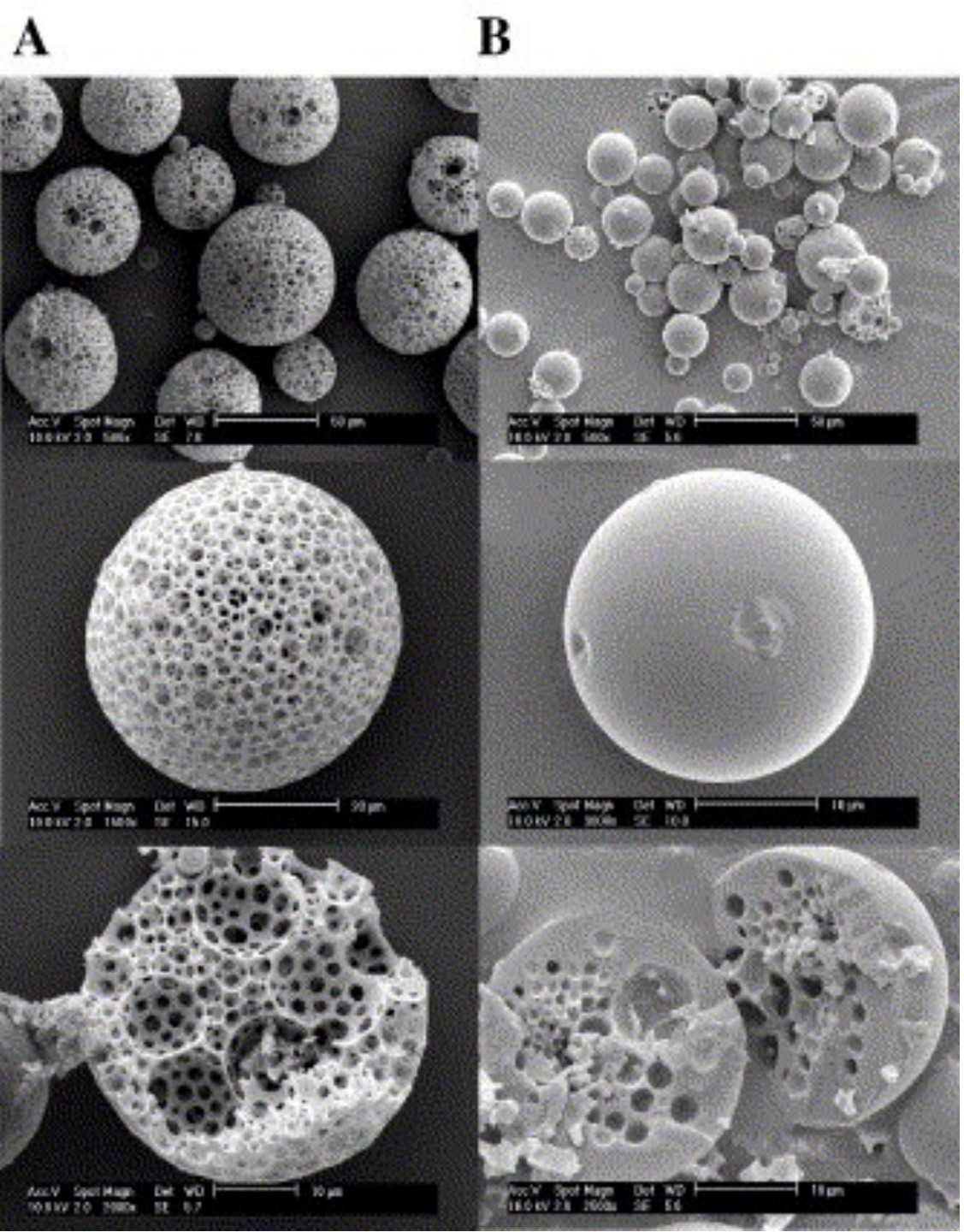


Fig. 4 SEM images of overall (upper row), surface (middle row) and cross-section (bottom row) of PLGA microspheres (A) porous microspheres and (B) pore-closed microspheres prepared by treating with ethanol vapor in a fluidized bed reactor.

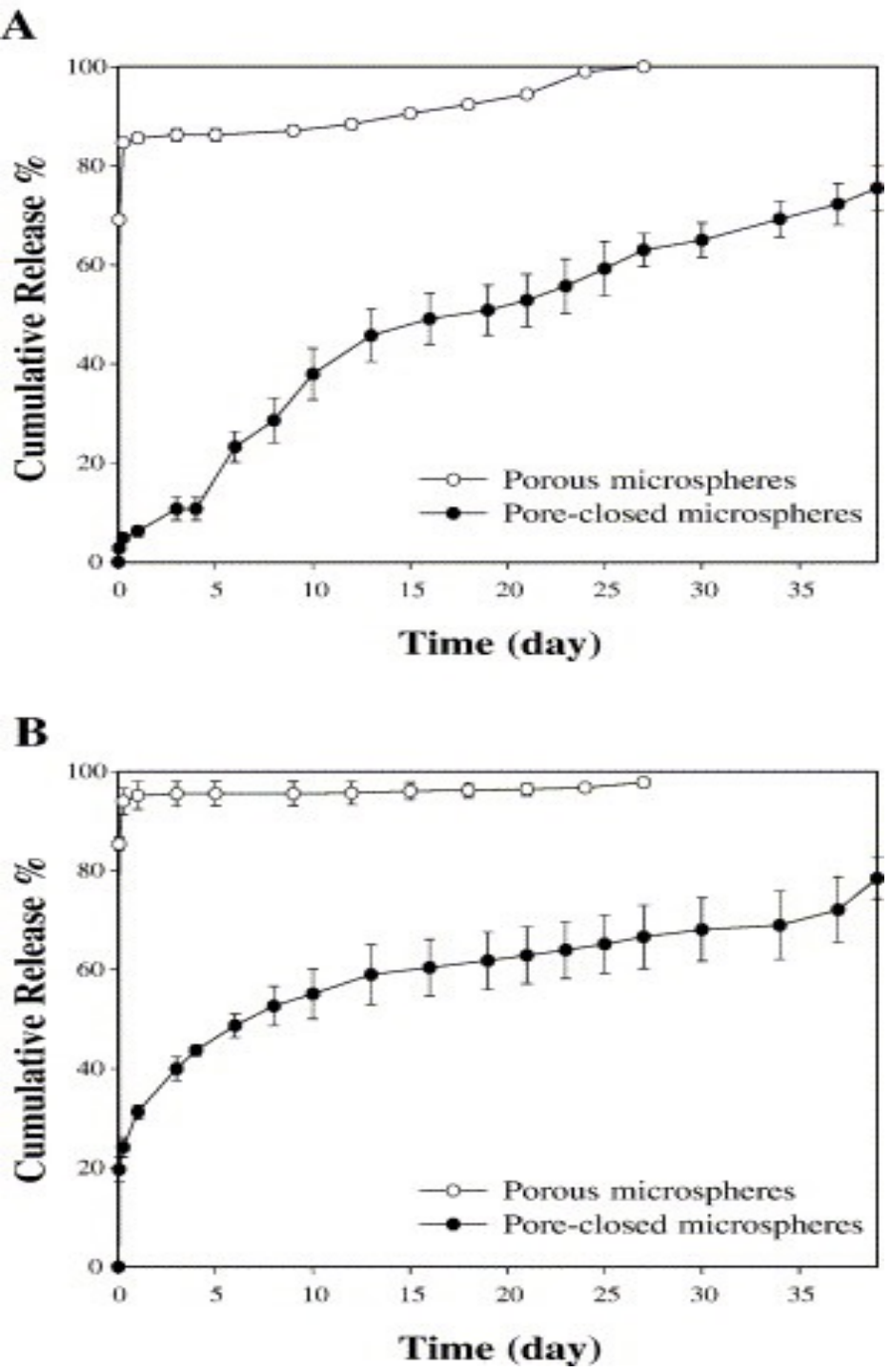


Fig. 5 In vitro release profiles of rhGH from porous and pore-closed microspheres with loading amounts of (A) 3.5<ce:hsp sp="0.12"/> ?<ce:hsp sp="0.12"/> 0.1% (w/w) and (B) 11.4<ce:hsp sp="0.12"/> ?<ce:hsp sp="0.12"/> 0.5% (w/w). Error bars show ...